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Genetic and epigenetic modifiers of metastasis: Context matters

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Review

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Abstract

This review summarizes evidence related to metastasis-associated genes and their functions. Their discovery, rigor of evidence for involvement in cancer metastasis, correlations and anticorrelations with metastatic propensity, biochemical function(s), and clinical associations are summarized and critically evaluated. What emerges is a picture whereby function is determined by context (tumor type, which in vivo or in vitro assays were used to assess function(s), whether RNA or protein is being measured, and redundancy of related molecules, cellular location, protein stability, etc.) due to differential regulation and interactions. Many metastasis genes have been implicated in individual steps of the metastatic cascade, while others impact multiple steps, complicating the ability to ascribe definitive mechanism(s) of action. Likewise, many metastasis-regulatory molecules are involved in multiple cellular signaling pathways due to interactions with other macromolecules. The implications of the complexity of metastasis genetics and epigenetics for prognosis and treatment are also briefly discussed.

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Overall objective and organization of this review

The review is organized into several broad categories. We begin by describing foundational principles of metastasis and tumor heterogeneity. This is followed by some of the earliest metastasis suppressor gene discoveries (nm23, KISS1, BRMS1) and how they were discovered. Their mechanisms of action are outlined along with some of the context-specific differences reported for each. Next, genes and gene products regulating epigenetic processes are presented, followed by RNA and protein translational regulation molecules. A brief segue will introduce background genetics and how they alter metastasis efficiency before summarizing molecules involved in adhesion, signaling, and invasion.

What has emerged is a clear conclusion that metastasis genetics is complex, multifactorial, and context dependent. Idiosyncrasies of each gene (and gene product) are still being worked out. Despite those complexities, significant progress has been made, and clinically translatable endpoints are coming more into focus (Steeg and Theodorescu, 2007; Steeg *et al.*, 2009; Gelman, 2023). Importantly, metastasis-associated genes control multiple cellular responses to different microenvironments. Indeed, some metastasis-associated molecules regulate the tissue microenvironment. As individual genes are described next, we have attempted to summarize key correlative findings as well as any disparities of findings in different tumor types and in different assays.

Throughout this review, we have attempted to minimize presentation of our bias regarding strength and weakness of specific data, preferring that readers make conclusions based on their experiences and incorporation of some as-yet-unreported data. While we have attempted to be relatively comprehensive, we acknowledge that some papers and findings are missing. Likewise, for practical reasons, we present some genes/gene products in greater depth, while others are included only to emphasize specific points and/or patterns. Our hope is that this critical analysis will highlight directions for future studies with these, and newly discovered, metastasis-associated genes.

In the end, this review provides a lot of information. We encourage readers to not focus on the details (unless they are of particular interest to you) since the major theme – the context dependency of metastasis gene function – will be lost. Rather, we suggest looking at vignettes illustrated by each of the genes, gene classes, or signaling pathways to demonstrate how the context matters. Location (tissue of origin and subcellular), isoforms and post-translational modifications, interactors (both cellular and molecular), regulators (signaling and epigenetic), and stability are all determinants of metastasis gene (product) mechanism(s) of action. Additionally, we encourage readers to consider the quality and availability of selective reagents and how those parameters have limited the ability to define mechanisms of action. As the field moves forward, careful integration of these currently disparate observations will reveal an accurate and holistic view of the metastatic process. From those new insights, improvements in cancer diagnosis and treatment will emerge.

Since this journal has a wide spectrum of readership, we have prepared supplemental tables of abbreviations and a list of commonly used cell lines that are cited in order to overcome specialty-specific jargon. Whenever appropriate, we have cited original articles rather than other summary reviews. Doing so, we hope that readers will be able to critically evaluate the claims made.

Metastasis biology

Metastasis involves dissemination of cells away from the original tumor via different routes – hematogenous (Fidler, 1978; Nicolson, 1988), lymphatics (Sleeman and Thiele, 2009; Nathanson *et al.*, 2018; Leong and Witte, 2024), across coelomic cavities (Lengyel, 2010; Clark *et al.*, 2013), along nerves (Marchesi *et al.*, 2010; Sleeman *et al.*, 2011; Roh *et al.*, 2015), and between endothelial cells and basement membranes (Lugassy *et al.*, 2004). All of these routes of metastasis are clinically important, but hematogenous metastasis (Figure 1) is most extensively studied since it is associated with development of visceral metastases. Dissemination involves motility of cancer cells that occurs by a variety of mechanisms in which cells utilize cell–cell and cell–matrix interactions (Wolf *et al.*, 2007; Yilmaz and Christofori, 2010; Friedl *et al.*, 2012; Simini *et al.*, 2012; Te Boekhorst *et al.*, 2016; Stuelten *et al.*, 2018; Mishra *et al.*, 2019; Parlani *et al.*, 2023; Garcia-Arcos *et al.*, 2024; Chastney *et al.*, 2025). Some of the motile cells move about haphazardly, while others are sometimes directed by chemotactic, haptotactic, or durotactic signals (Rieppi *et al.*, 1999; Luangdilok *et al.*, 2007; Su *et al.*, 2010; Stuelten *et al.*, 2018; Chitty *et al.*, 2026). Recent evidence suggests that subsets of cancer cells serve as pioneers, while others follow leader cells (Konen *et al.*, 2017; Khatib *et al.*, 2025; Wan *et al.*, 2025). Invasion, as the defining feature of malignancy, describes the capacity for neoplastic cells to penetrate basement membranes and stroma. Invasion often involves degradation of matrices (Stetler-Stevenson *et al.*, 1993; Mason and Joyce, 2011; Radisky, 2024), but proteolytic cleavage of the extracellular matrix (ECM) is not always required (Wolf *et al.*, 2003; Wolf and Friedl, 2006; Te Boekhorst *et al.*, 2016). While invasion is required for metastasis, it is not sufficient for cells to metastasize.

Metastasis is recognized as the primary contributor to cancer morbidity and mortality (Welch and Hurst, 2019), but it is not the only cause of cancer deaths (Boire *et al.*, 2024). When cancers are detected early, survival rates improve dramatically. However, if the cancer has already spread, cure rates drop sharply. Fortunately, not all cancers metastasize. Some cancers are highly aggressive, establishing secondary lesions with high frequency (e.g., melanoma, pancreatic ductal adenocarcinoma, small cell carcinoma of the lung). Other cancers rarely metastasize despite being locally aggressively

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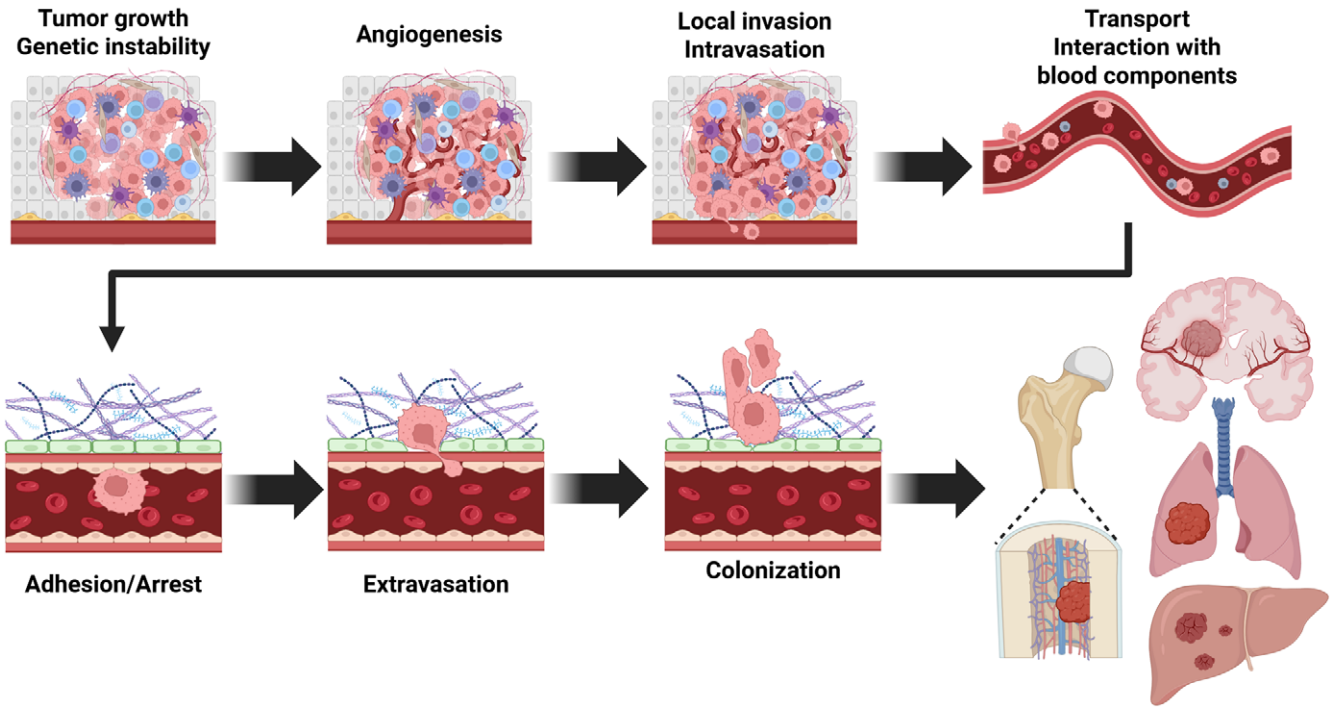


Figure 1. The pathogenesis of blood-borne metastasis. Although metastases can arise by dissemination via multiple routes, hematogenous spread is considered especially important because it results in widespread seeding of cells to multiple visceral, vital organs. Metastatic cells arise from heterogeneous populations of neoplastic cells which arose as a result of genomic instability and epigenetic responses to the tumor microenvironment (TME). The cancer cells likewise influence the TME by inducing new vessels (angiogenesis), which are commonly less patent and more convoluted. Competent neoplastic cells invade locally, eventually intravasating into thin-walled vessels, where they enter circulation. During transport, cells are susceptible to sheer and attack by immune cells as well as cooperation with platelets and other blood components. Individual cells or cell clusters (homotypic or heterotypic) adhere to endothelial surface molecules or become trapped by their inability to squeeze through small vessels. Arrested cells then exit the vessels (extravasate) and, if they have arrived at permissive sites and can respond favorably to new TME, they proliferate and colonize secondar tissues.

invasive (e.g., basal cell carcinomas of the skin, glioblastoma multiforme) (Esserman and Varma, 2019). Some argue that invasion is recapitulation of an embryonic process – the epithelial–mesenchymal transition (EMT) (Thiery, 2002). EMT allows dissociation of epithelial cells by acquisition of mesenchymal characteristics (Chaffer *et al.*, 2016; Lambert *et al.*, 2017). Concomitantly, cells undergoing EMT acquire stem-like characteristics that will be required for proliferation at secondary sites (Mani *et al.*, 2008; Lambert *et al.*, 2017). The EMT theory also includes reversion to an epithelial phenotype, so cells can resume proliferation. The reversion is termed the mesenchymal–epithelial transition (MET) (Chaffer *et al.*, 2006; Tsai *et al.*, 2012a). However, it is important to recognize that EMT is not exclusively bimodal. There is a continuum of phenotypes exhibiting characteristics of the epithelial and mesenchymal states (Bakir *et al.*, 2020; Graziani *et al.*, 2022; Zhang *et al.*, 2025a). Likewise, cooperative migration of cell clusters often observed in histologic sections argues for relatively common retention of cell–cell junctions (Saitoh, 2018).

Abundant evidence supports roles for EMT in carcinomas, but a few experiments point to the nonuniversality of EMT as a requirement for cancer metastasis. Tsuji *et al.* isolated and generated cell lines from a single tumor which were stable for either epithelial or mesenchymal characteristics (Tsuji *et al.*, 2008, 2009). Neither population successfully completed the metastatic cascade when injected individually. However, when coinjected, both cells were found in metastases. In other studies that utilized reporter genetic constructs activated when cells underwent EMT, metastases were formed even when cells had not undergone intervening EMT (Fischer *et al.*, 2015; Zheng *et al.*, 2015). Therefore, while EMT is a means to metastasis, it is neither necessary nor sufficient.

Following invasion into blood, lymphatics, or body cavities, neoplastic cells must survive sheer forces (Krog and Henry, 2018) and immune cell killing (Delclaux *et al.*, 2024; Goddard *et al.*, 2024; Dai *et al.*, 2025). Surviving cells eventually arrest as single cells or emboli when vessel diameters become too small to traverse (Fidler, 1970, 1973a; Updyke and Nicolson, 1986). Or they selectively recognize and adhere to plasma membrane molecules on vessel walls (endothelium) or tissue linings which represent cellular "addresses" (Alby and Auerbach, 1984; Auerbach *et al.*, 1987; Belloni and Nicolson, 1988; Belloni and Tressler, 1989; Pasqualini and Ruoslahti, 1996; Pasqualini *et al.*, 2002). Following arrival at secondary sites, cells must eventually proliferate to form secondary masses in order to be called a bona fide metastasis (Welch and Hurst, 2019; Gerstberger *et al.*, 2023).

Colonization, the last step in the metastatic cascade, involves co-option of existing vessels, angiogenesis, or the formation of vascular channels by tumor cells themselves (Hendrix *et al.*, 2003; Folkman, 2006; Naumov *et al.*, 2008). Emerging evidence suggests that signals from a primary tumor create a niche which subsequently disseminated cells depend upon for eventual survival and proliferation (Kaplan *et al.*, 2006; Psaila and Lyden, 2009; Peinado *et al.*, 2017). The nature of these premetastatic niches varies and can involve bone marrow progenitors (Kaplan *et al.*, 2005; Lucotti *et al.*, 2025), myeloid-derived suppressor cells (Psaila and Lyden, 2009), neutrophils (Wculek and Malanchi, 2015; Albrengues *et al.*, 2018), and neutrophil extracellular traps (Demers *et al.*, 2012; Cedervall

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et al., 2016; Lee *et al.*, 2025; Shahzad *et al.*, 2026). Importantly, the niches alter the microenvironment and allow cells that have arrived to thrive and proliferate in the new location (Deasy and Erez, 2022; Mukherjee and Bravo-Cordero, 2023; Nowosad *et al.*, 2023; Patras *et al.*, 2023; Monteran *et al.*, 2024; Wu *et al.*, 2024; Lucotti *et al.*, 2025; Parida and Malladi, 2025; Thakur *et al.*, 2025). However, it is important to note that metastases can subsequently metastasize as well (Fidler and Nicolson, 1977).

Colonization of secondary (or higher order) sites does not require immediate cell division. Cancer cells can remain dormant for years following seeding (Yeh and Ramaswamy, 2015; Gay and Malanchi, 2017; Aguirre-Ghiso and Sosa, 2018; Chiu *et al.*, 2023; Tau and Miller, 2023; Truskowski *et al.*, 2023; Agudo *et al.*, 2024; Tomasin and Ghajar, 2024; DeMichele *et al.*, 2025). From a clinical perspective, dormancy simply means that the volume of tumor cells is below the limit of detection using current imaging or biochemical assays. From a mechanistic perspective, dormancy is critically important. There is considerable interest in maintaining cells in a latent state as it could lengthen the asymptomatic or a symptomatic phase of cancer which is more tolerable, allowing patients to live longer while retaining a high quality of life (Werner-Klein and Klein, 2019; Agudo *et al.*, 2024).

For many years, metastasis was considered the ultimate stage of tumor progression, that is, it occurs late in the pathobiology of neoplasia. However, several recent studies have introduced some doubt into that conclusion. Namely, cancer cells can begin disseminating long before a primary tumor is detectable (Husemann *et al.*, 2008; Friberg and Nystrom, 2015; Harper *et al.*, 2016; Hosseini *et al.*, 2016). Fortunately, the metastatic process is highly inefficient (Weiss, 1990). But the possibility that cells exist systemically – even if not detectable at the time of diagnosis – alters treatment options and strategies. As a result, the underlying mechanisms leading to any of the earlier steps of metastasis will be pivotal to improving treatment outcomes. It is to that end that we submit this review.

Heterogeneity of cancer and metastasis

Another important tenet regarding metastasis derives from the long-recognized heterogeneity that exists within every neoplasm (Hunter *et al.*, 2018) and metastasis (Yang *et al.*, 2026). Behavioral and morphologic differences are due to genetic, epigenetic, positional, or temporal variations (Welch, 2016). Genetic heterogeneity is defined by inherent and relatively stable properties for a given phenotype. Epigenetic heterogeneity is characterized by transient chemical modifications of DNA or chromatin that alter gene transcription in a spatial and temporal manner. Critically, most metastases are clonally derived (Wolman *et al.*, 1985; Fidler and Talmadge, 1986; Yamamoto *et al.*, 2003; McGranahan and Swanton, 2017) and the cells that eventually colonize ectopic sites can be selected for (Fidler, 1973b). Since a small fraction of cells successfully metastasize and since the signal-to-noise ratio for biochemical, genetic, and epigenetic changes in that small population could be masked by the majority of cells, progress in identifying the underlying mechanisms of metastasis has been painstakingly slow. The mixed compositions of metastases can be explained by inherent genetic and genomic instability of neoplastic cells, movement of cells between metastases, seeding by late-arriving cells, and differential responses of cells within the metastasis to external signals. Nonetheless, substantial progress has been made.

As one explores the underlying genetics of metastasis, another caution is advised. Metastasis is a complex genetic disease. By *complex disease*, we refer to any disease or disorder that involves the interplay of multiple genes (termed quantitative trait loci, QTL), each contributing a small part to the whole (reviewed in Cookson *et al.*, 2009; Qi *et al.*, 2024). Of the steps outlined earlier, a successful metastatic cell must possess all those characteristics. For if a cell cannot complete any step in the metastatic cascade, it cannot proceed to subsequent steps. Moreover, complex diseases occur on different genetic backgrounds which amplify or mute specific genetic or epigenetic changes in the cancer cells (Medicine NAoSEa, 2023). When coupled with environmental influences, assessment of the impacts of specific genes and molecules is daunting.

Metastasis genetics, like cancer genetics, can be categorized in different ways. Analogous to genes (and gene products) that either increase or decrease neoplastic transformation, there are genes/products that enhance or suppress metastatic efficiency. Nguyen *et al.* categorize them in a slightly different way. They categorize metastasis genes by when they are involved in metastasis – initiation (invasion, angiogenesis, bone marrow mobilization, and circulation), progression (extravasation, survival, and reinitiation), and virulence (organ-specific colonization) (Nguyen *et al.*, 2009). Either way, the categorizations are arbitrary since most metastasis-associated genes function in multiple processes involved in the continuum of the metastatic cascade.

Unfortunately, the nature of the metastatic cascade makes definitive identification (and classification) of metastasis-promoting molecules more technically challenging. Successful metastatic cells are likened to decathletes who must succeed in all events, though not necessarily the winner of every event. If a decathlete cannot complete one of the events, (s)he cannot win the decathlon. By analogy, if a metastatic cell cannot complete any step of the metastatic cascade, it cannot proceed to the next event and is therefore nonmetastatic. Thus, to test prometastatic effect, one must know that the cell in which that gene (product) is being tested is capable of completing the other steps of the metastatic cascade. Otherwise, the experimentalist will receive a false-negative result. In contrast, a metastasis suppressor needs to inhibit only one step to render a cell nonmetastatic. As a result, discovery of metastasis suppressors has outpaced discovery of promoters.

Identification of metastasis-associated genes

Identification of metastasis-associated genes has been accomplished using several different approaches, some functional in nature, while others are purely correlative in nature. Some methods used to identify metastasis regulatory genes include subtractive hybridization, microcell-mediated chromosome transfer, genetic selections, comparison of genetic polymorphisms (reviewed in Shevde and Welch, 2003; Hurst and Welch, 2011a; Bohl *et al.*, 2014; Gelman, 2023; Khajehdehi, 2025). New tools have built datasets of genes whose expression (mostly RNA) is correlated with metastatic efficiency (Ghandi *et al.*, 2019; Jin *et al.*, 2020). The approaches which have demonstrated function (i.e., a positive or negative effect on metastasis) are prioritized herein, while the correlations await functional validation. That said, a theme of this review is the fact that functional characterization is highly dependent on the context in which the molecule(s) or pathway(s) is tested. The tissue origin of the cancer cell, the genetic background of the animal (or human) from which the cancer cell is derived, and the immune status of the animal in which metastatic potential is measured are all parameters that impact results.

Those contexts determine how metastasis-associated genes are regulated. One can think of that regulation in terms of epigenetics. At a 30,000-foot view, epigenetics integrates individual genes with

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how they respond to different microenvironmental queues requiring coordinated expression of genes at every step (Fidler *et al.*, 2007; Langley and Fidler, 2011; Sleeman *et al.*, 2011; Hurst and Welch, 2011b; Bragado *et al.*, 2013; Obenauf and Massague, 2015). The importance of a metastatic cell's response to external signals is highlighted by the context-specific functionality of metastasis-associated genes. Likewise, responsiveness to different microenvironments helps explain one of the hallmarks of metastasis, plasticity (Welch and Hurst, 2019).

The epigenetic landscape was first characterized by Conrad Waddington in 1942 (Waddington, 1942). Epigenetic regulation is accomplished by chemical modifications to DNA and/or chromatin-associated histones (Rodriguez-Paredes and Esteller, 2011). Gene transcription is regulated by manipulation of the three-dimensional structure of DNA. Histone acetyltransferases (HAT) add acetyl moieties to lysine side chains of histones, while (de)acetylation is accomplished through histone deacetylases (HDAC). The former generally results in an open conformation of DNA (euchromatin), while the latter compacts DNA (heterochromatin) and represses transcription. HAT and HDAC complexes are large and are often linked with DNA methyltransferases and other protein or DNA-modifying enzymes. Over time the epigenetic landscape has been expanded to include ≥17 DNA modifications (Lowe *et al.*, 2021), >150 RNA modifications (Chen *et al.*, 2016a; Shi *et al.*, 2019), >100 histone modifications (Zhao and Garcia, 2015) (commonly called the 'histone code' (Jenuwein and Allis, 2001; Strahl and Allis, 2000)), >20 histone variants (Buschbeck and Hake, 2017; Martire and Banaszynski, 2020), a seemingly ever-growing number of noncoding RNA (Consortium, 2004; Anastasiadou *et al.*, 2018), and families of regulatory proteins categorized as writers, erasers, readers, chromatin remodelers, and histone chaperones (Huether *et al.*, 2014; Lawrence *et al.*, 2014; Leiserson *et al.*, 2015; Feinberg *et al.*, 2016).

Nm23/NME1

The first metastasis suppressor, nm23 (NME1, NDPK, nucleoside diphosphate kinase), was discovered by Patricia Steeg who used differential expression to isolate it from poorly metastatic K1735 melanoma cells (Steeg *et al.*, 1988). When re-expressed in variants of those melanoma cells, NME1 suppressed metastasis. She and others identified similar correlations between *NME1* expression and reduced metastasis and improved patient survival (Bevilacqua *et al.*, 1989; Florenes *et al.*, 1992; Royds *et al.*, 1993; Tokunaga *et al.*, 1993; Nakopoulou *et al.*, 1999; Goncharuk *et al.*, 2004; Chen *et al.*, 2020b). High expression of *NME1*, however, is reported as a prognostic factor for unfavorable outcome in liver, lung, and renal TCGA (The Cancer Genome Atlas Program) data accessed via Human Protein Atlas (Uhlen *et al.*, 2010). Elevated expression of NME1 was observed in advanced thyroid carcinoma by stage (Zou *et al.*, 1993) and STAD lymph node metastases (Muta *et al.*, 1994). As with other metastasis suppressors, the effects are histotype specific (Hailat *et al.*, 1991; Haut *et al.*, 1991; Niitsu *et al.*, 2001; Andolfo *et al.*, 2011).

NME1 was the first of a family of 10 molecules possessing NDPK catalytic activity. NDPK enzymes synthesize phosphohistidines using ATP as a donor (Hartsough *et al.*, 2002; Klumpp and Krieglstein, 2009; Khan and Steeg, 2018). The isoforms are found in multiple cellular pathways, vary in size and cellular localization. These pleiotropic properties have contributed to difficulties definitively determining the antimetastatic mechanism(s) of action.

Genetically engineered mouse models have been developed for NDPK family members (Arnaud-Dabernat *et al.*, 2003; Postel *et al.*, 2009; Di *et al.*, 2010; Vogel *et al.*, 2010). Whole-body knockout and mutant mice display isotype-specific different developmental defects, including mammary gland and neuronal development and maturation, immune system dysfunction, cytokine production, and perinatal lethality. Boissan *et al.* (2005) crossed NME1-knockout mice with transgenic mice that develop hepatocellular carcinoma and observed increased lung metastases. Relatedly, orthologs of NME1 in *Drosophila* and *Dictyostelium* have illuminated the existence of subgroups of NDPK and differentiated the ability of human genes to complement genetic defects (reviewed in Matyasi *et al.*, 2020). Collectively, findings in those models have helped define NDPK family clusters and differential activities but have contributed relatively less to determining the mechanism of action responsible for NME1 metastasis suppression. Identification of binding partners has, however, helped refine roles for NME1 in various steps in the metastatic cascade.

Silencing NME1 increases intercellular adhesion, motility, and invasion through extracellular matrices concomitant with increased MMP secretion, RAC, MAPK, and PI3K/AKT signaling (Boissan *et al.*, 2010). NME1 can bind Dbl-1 which, in turn, inactivates Cdc42 to inhibit motility (Murakami *et al.*, 2008). NME1 binding to gelsolin, thereby disrupting its actin-severing capacity, also disrupts motility and invasion (Garzia *et al.*, 2006; Marino *et al.*, 2013). NME1 can also inhibit invasion by disrupting TGFβ-induced EMT and invasion (Welch *et al.*, 1990a, 1990b; Welch and Hurst, 2013; Zhao *et al.*, 2013). And finally, NME1 binding to Dynamin (an atypical GTPase) was identified by binding of the *Drosophila* ortholog of NME1, AWD, to Shibire, the Dynamin ortholog. Dynamin is required for endocytic vesicle generation, and disruption of its function is thought to impede cellular responses to chemotactic factors (Boissan *et al.*, 2014; Khan *et al.*, 2019; Prunier *et al.*, 2023). The latter functions also imply that NME1 can regulate other functions associated with membrane engulfment and phagocytosis, like apoptosis.

Among the most intriguing interactions for NME1 is with kinase suppressor of Ras (KSR), a family of scaffolds which promote assembly of Ras/Raf/Mek/Erk complexes (Downward, 1995; Kornfeld *et al.*, 1995; Raabe and Rapp, 2002). By those interactions, NME1 inhibits MAPK activity. Since the Ras/Raf/Mek/Erk pathway is a significant proliferation signal, the KSR and NME1 interactions are suspected to play roles in proliferative aspects of the metastatic cascade, such as colonization. Further evidence for this suspicion is the negative correlation between NME1 expression and lysophosphatidic acid receptor 1 expression, the latter of which shifts the p38:ERK ratio toward dormancy (Aguirre-Ghiso *et al.*, 2003).

Although mostly cytoplasmic, NME1 and NME2 are also found in the nucleus. Those findings suggest additional mechanisms of action. The *Drosophila* ortholog, Awd, exhibits exonuclease activity to supercoiled DNA, but not double-stranded or single-stranded DNA (Qian and Liu, 2014). Both NME1 and NME2 (also known as PuF) can bind to single-stranded promoter regions to regulate transcription as coregulators. Both NME1 and NME2 interact with other transcription factors (Roymans *et al.*, 2002). Both NME1 and NME2 are associated with estrogen receptor alpha (ERα) to differentially regulate estrogen-responsive genes (Curtis *et al.*, 2007; Rayner *et al.*, 2007, 2008). Similarly, interactions between NME1 and NME2 are implicated in the regulation of other metastasis-associated genes, such as COX2 through interactions with NFκB and CREB (Subramanian and Robertson, 2002). NME1 also binds

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GATA-1 and EBNA3C to bind SP1 complexes to regulate alpha V integrin (Choudhuri *et al.*, 2006). Kaetzel and colleagues elaborate in more detail the transcriptional properties of NME1 and NME2 as well as their potential roles in DNA repair (Puts *et al.*, 2018).

Just as with the other metastasis suppressors, the numbers of mutations found in cancer cells or human cancers are vanishingly small. The diminished expression of metastasis suppressors appears to be mostly via epigenetic mechanisms, most of which are still not fully characterized but indeed occur by multiple mechanisms of regulation (Sethi and Kang, 2011; Bohl *et al.*, 2014; Liu *et al.*, 2014c; Vivian *et al.*, 2017, 2018). Such epigenetic regulation is key to the plasticity hallmark of metastasis (Welch and Hurst, 2019).

KISS1, CRSP3, and TXNIP

Discovery of the KISS1 metastasis suppressor began with the recognition that metastatic human melanomas frequently lost copies of the long arm of chromosome 6 (Trent *et al.*, 1989; Fountain *et al.*, 1990; Trent, 1991). Using microcell-mediated chromosome transfer, Welch *et al.* (1994) introduced a complete chromosome 6 into metastatic C8161 melanoma cells resulting in the hybrid cells being completely suppressed for metastasis. Then, by comparing parental C8161 and chromosome 6 cells using differential display, Lee identified several mRNA more highly expressed in the metastasis-suppressed hybrids (Lee *et al.*, 1996, 1997). The first characterized gene was designated KISS1 in honor of its discovery in Hershey, Pennsylvania. When transfected into metastatic melanoma (Lee *et al.*, 1996; Nash *et al.*, 2007) and breast carcinoma cells (Lee and Welch, 1997), KISS1 suppressed metastasis without blocking primary tumor formation. Subsequently, other laboratories transfected KISS1 into PRAD (Wang *et al.*, 2012a), HNSC (Jiffar *et al.*, 2011), PAAD (McNally *et al.*, 2010), and OVCA (Hori *et al.*, 2001) cancer cell lines with similar result, firmly establishing KISS1 as a bona fide metastasis suppressor. [Note: for space reasons, we will use the TCGA abbreviations to refer to specific tumor types for the remainder of this review. However, readers are cautioned that some cancer subtypes are not denoted in all cases.]

Correlative clinical studies have similarly demonstrated that *KISS1* expression is inversely correlated with neoplastic aggressiveness, invasion, and/or metastasis (Yan and Boyd, 2000; Yan *et al.*, 2001; Zheng *et al.*, 2010, Teng et al., 2011, 2013; Zhang *et al.*, 2014a; Li *et al.*, 2020). In other histotypes, however, higher KISS1 expression is correlated with enhanced aggressiveness and metastasis (Savvidis *et al.*, 2015; Guzman *et al.*, 2018; Tian *et al.*, 2018; Kim *et al.*, 2022; Pupaki *et al.*, 2022; Shah *et al.*, 2025a). The reasons behind this discrepancy are not understood; yet, they highlight a key theme of genetic complexity and context dependency.

Defining how KISS1 suppresses metastasis has been challenging for a multitude of reasons. Unexpectedly, *KISS1* maps to chromosome 1q32 (West *et al.*, 1998). Reasoning that the losses of genes on chromosome 6 were regulators of *KISS1*, Miele *et al.* used the microcell-mediated transfer of chromosome 6 structural mutants to identify putative regulatory loci (Goldberg *et al.*, 2003). Eventually, they identified a 40-cM region between 6q16.3-q23 as the principle regulatory region of *KISS1* (Miele *et al.*, 2000). Those results were subsequently confirmed by (Shirasaki *et al.*, 2001). To identify upstream regulator(s) of KISS1, microarrays comparing C8161 and the chromosome 6 hybrid variants were performed (Goldberg *et al.*, 2003). Those arrays identified another molecule encoded on chromosome 1, TXNIP/VDUP1 (thioredoxin binding protein 2 or vitamin D upregulated protein 1), that was found to also be more highly expressed when the region between 6q16.3-q23 was present. Further refinement of the region on chromosome 6 identified a transcription coactivator, *MED23* (also known as *ARC130*, *CRSP130*, *CRSP133*, *CRSP3*, *DRIP130*, *MRT18*, *SUR-2*, *mediator complex subunit 23*), which increased expression of both *KISS1* and *TXNIP*. Re-expression of *TXNIP* alone upregulated *KISS1* expression and suppressed metastasis. These studies identified a complex, apparently coordinated pathway that regulates cancer metastasis. Still, however, the mechanism by which this pathway suppresses metastasis has yet to be worked out despite corroboration of roles of TXNIP in tumor/metastasis suppression in other tumor types (Ohta *et al.*, 2005; Masaki *et al.*, 2012; Morrison *et al.*, 2014; Singh *et al.*, 2025).

Early experiments showed that KISS1 re-expression blocked metastasis in vivo but caused modest or no effects on metastasis-associated phenotypes in vitro (Lee *et al.*, 1996; Lee and Welch, 1997). Adding to the difficulty was the inability to detect KISS1 protein. The latter issue was resolved when Ohtaki *et al.* (2001) identified a C-terminal peptide derived from KISS1 as the ligand for an orphan G-protein-coupled receptor. The fragment was originally named metastin, but a more standardized nomenclature has been subsequently adopted.

Another emerging complication related to the assessment of KISS1 function in cancer metastasis is the existence of SNP (single-nucleotide polymorphism) that might impact function (Malik *et al.*, 2008; Pentheroudakis *et al.*, 2010; Nazir *et al.*, 2011; Ruiz *et al.*, 2012; Cruz Quevedo *et al.*, 2015; Quevedo *et al.*, 2015; Roberts *et al.*, 2017; Antar *et al.*, 2020). Similar SNP are present in KISS1R (Teles *et al.*, 2010; Zhao *et al.*, 2022; Toutoudaki *et al.*, 2023; Zhang *et al.*, 2023b; Ruiz and Ramos, 2024; Zouaghi *et al.*, 2024). Both polymorphisms are better characterized in noncancer contexts but need to be thoroughly assessed in cancer contexts as well.

Nascent KISS1 is a 145-amino acid secreted polypeptide which is processed extracellularly by the prohormone convertase furin (Harihar *et al.*, 2014). The resulting fragments are referred to as kisspeptins (KP). Metastin, the predominant fragment, is a 54-amino acid polypeptide (aa68–aa121) now designated KP54 or KP-54. KP54 can be further cleaved into smaller (13, 14, or 10 amino acids) KP from the (typically amidated) C terminus (Kotani *et al.*, 2001). Whenever the smaller KP retain the terminal RF–NH_2 sequence, they can bind to and activate the KISS1 receptor (KISS1R, also known as AXOR12, GPR54, or hOT7T175) (Kotani *et al.*, 2001; Muir *et al.*, 2001; Navarro and Tena-Sempere, 2011). In several publications, the smallest KP, KP-10, has been shown to be sufficient for full KISS1R activation. Due to the ease of manufacturing of smaller peptides, KP10 has become the predominant reagent used to study KISS1/KISS1R functions (reviewed in Tsoutsouki *et al.*, 2022; Shah *et al.*, 2025b). Some of those studies will be summarized next.

A critical characteristic of KISS1 is that it appears to function in a paracrine manner. If the signal peptide is removed, KISS1 is no longer able to suppress metastasis (Nash *et al.*, 2007). However, that observation is paradoxical since none of the cell lines in which KISS1 re-expression led to metastasis suppression express the KISS1R. As a result, the existence of another KISS1 receptor is predicted to exist (Beck and Welch, 2010). Although such a receptor is possible since there are other KISS1 and KISS1R family members in mammals and other species (Kim *et al.*, 2012; Salmeri *et al.*, 2024; Stoynev and Kumanov, 2025), no orthologs in humans have been described. The roles of those molecular siblings have not been well explored in the context of cancer but have been more extensively studied in relation to KISS1's functions in the hypothalamic–pituitary–gonadal axis

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(reviewed in Millar and Babwah, 2015; Ruohonen *et al.*, 2020; Tsoutsouki *et al.*, 2022; Greenhill, 2023; Stoynev and Kumanov, 2025).

KISS1/KP54 activates a variety of signals, including phospholipase C (PLC), protein kinase C, intracellular Ca^{2+} mobilization, and mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT pathways (Beck and Welch, 2010). All of these signaling pathways have been implicated in multiple hallmarks of cancer and metastasis, making it challenging to dissect the specific roles for KISS1 in suppressing metastasis. Nonetheless, some nuggets of information have emerged from an unexpected finding in which KISS1-expressing cells appear to reverse a process termed aerobic glycolysis (Liu *et al.*, 2014b).

Otto Warburg was among the first to recognize the contributions of metabolic reprogramming in cancer (Warburg *et al.*, 1927; Warburg, 1956a, 1956b). That property of cancer cells has been repeatedly observed and is now recognized among the so-called hallmarks of cancer (Hanahan and Weinberg, 2000, 2011). The mechanisms underlying Warburg's observations of aerobic glycolysis have been the subject of countless studies (reviewed in Thompson, 2009; Vander Heiden *et al.*, 2009; Ward and Thompson, 2012; Vander Heiden and DeBerardinis, 2017; Pavlova *et al.*, 2022; Altieri, 2023). Collectively, the data suggest that cancer cells are remarkably plastic with regard to their utilization of metabolic pathways. Efficiency of the generation of energy (i.e., ATP) is sometimes subjected to prioritized generation of macromolecules necessary for cell division. Likewise, neoplastic cells shift energy sources (Thompson, 2009; Vander Heiden *et al.*, 2009; Sullivan *et al.*, 2016).

Cells expressing KISS1 increased extracellular pH in vitro by decreasing aerobic glycolysis. Liu *et al.* (2014b) eventually showed that KISS1 alters mitochondrial respiration and biogenesis by regulating PPARγ coactivator-1 (PGC1α). PGC1α regulates metabolism by increasing mitochondrial oxidative phosphorylation by inducing expression of genes in the citric acid cycle and electron transport chain (Ventura-Clapier *et al.*, 2008) via induction of the transcription factors NRFs and mtTFA (Girnun, 2012). Multiple other studies show that PGC1α is less expressed in neoplastic cells compared to matching normal tissues (Lehman *et al.*, 2000; Feilchenfeldt *et al.*, 2004; Watkins *et al.*, 2004; Zhang *et al.*, 2007; D'Errico *et al.*, 2011; Zuo *et al.*, 2021; Zhao *et al.*, 2023). However, there are also studies showing the opposite correlation (LeBleu *et al.*, 2014; Ganesan *et al.*, 2023), raising questions about the precise role(s) of PGC1α in cancer (Mastropasqua *et al.*, 2018). Notably, PGC1α also regulates anabolic metabolism. KISS1 re-expression also changed expression of genes involved in β oxidation (PPARα downregulation) and lipogenesis (FASN, ACC1 upregulation). KISS1-expressing cells also have lower V-ATPase expression, resulting in an attenuated v-ATPase activity (which is required for autophagy) (Manley *et al.*, 2017). KISS1-expressing cells exhibit reduced autophagy, but the context for autophagic differential regulation was not studied. Nonetheless and collectively, multiple findings establish links between KISS1, mitochondrial signaling, metabolism, and metastasis. However, those links are confused by the findings in cells not expressing the KISS1R.

A key clue regarding KISS1 mechanism of action was when Harms and Goldberg observed that KISS1-expressing cells were found to complete the entire metastatic cascade, except growth at secondary sites (Goldberg *et al.*, 1999). This in vivo result was consistent with previous in vitro experiments showing essentially no inhibition of growth, adhesion, invasion, etc. Interestingly, viable KISS1-expressing cells could be isolated from the lungs of mice weeks (and months) following the timeframe of when nonexpressing cells killed the mice. Imaging the lungs showed that KISS1-expressing cells had remained dormant at ectopic sites but would grow when implanted at an orthotopic site. So, from a functional perspective, a mechanism of action for KISS1 has been reported. However, the molecular basis for location specific growth regulation remains a mystery.

Although a bit tangential from the theme of this review, we note that KISS1 has been implicated in other diseases, most notably hypogonadism (Seminara *et al.*, 2003; Sam and Dhillo, 2010; Babwah *et al.*, 2015; Roa *et al.*, 2022). In that context, KISS1 is a neurotransmitter in the hypothalamic–pituitary–gonadal axis via the KISS1R. KISS1/KISS1R are also implicated in studies of polycystic ovary disease (Chen *et al.*, 2010; Lee *et al.*, 2010; Tang *et al.*, 2019; Araujo *et al.*, 2020; Daghestani *et al.*, 2020; Aasif *et al.*, 2023; Zheng *et al.*, 2026), atherosclerosis (Watanabe and Sato, 2020), myasthenia gravis (Lu *et al.*, 2025a), diabetes (Sliwowska *et al.*, 2024), obesity (Stephen *et al.*, 2024), and rheumatic arthritis (Wang *et al.*, 2021a). Recent data suggest that KISS1 may help distinguish responders versus nonresponders to immunotherapies (Wu *et al.*, 2026). Perhaps insights from those diseases will provide additional clues regarding KISS1 function in cancer. Nonetheless, aptamers and related treatments targeting KISS1 and KISS1R have been introduced into the clinic and are showing efficacy (MacLean *et al.*, 2014; Singh *et al.*, 2022; Tsoutsouki *et al.*, 2022; Shah *et al.*, 2025b; Velmurugan *et al.*, 2025; Kong *et al.*, 2026). While they have not been used in the context of cancer to the best of our knowledge, those treatments support the potential for KISS1-based therapies to be safely introduced in the future. Furthermore, they support the notion that treatments based on metastasis suppressors are possible (Gelman, 2023).

The implication that KISS1 could be used in cancer treatment is supported by recent observations that its expression is an immunotherapy biomarker (Wu *et al.*, 2026). Likewise, the observation that KISS1 could induce dormancy of tumor cells at ectopic sites suggests that a dormancy-based treatment, in which cancer is not necessarily cured, but is controlled, has become increasingly possible. In fact, recently reported results from Chodosh *et al.* demonstrate that it may be possible to identify dormant disseminated tumor cells and regulate their growth status (Dalla *et al.*, 2023; Sreekumar *et al.*, 2024; DeMichele *et al.*, 2025).

Epigenetic regulation of metastasis

BRMS1

BRMS1 (*BR*east cancer *M*etastasis *S*uppressor *1*) was discovered using differential display by Seraj *et al.* (2000c) by comparing metastatic MDA-MB-435 breast carcinoma cells with metastasis-suppressed microcell hybrids containing an introduced chromosome 11 (Phillips *et al.*, 1996). *BRMS1* maps to chromosome 11q13.1-13.2 (Samant *et al.*, 2000; *Seraj et al.*, 2000b; Samant and Welch, 2002; Zimmermann and Welch, 2020), a region often lost in late-stage breast cancers (Welch and Wei, 1998). When BRMS1 was transfected into MDA-MB-435 cells, metastasis was suppressed without significant changes in orthotopic tumor incidence. Subsequently, multiple laboratories have demonstrated BRMS1-mediated metastasis suppression in a variety of tumor types, including SKCM, BRCA, OV, READ, CHOL, STAD, and nonsmall cell lung carcinomas (NSCLC) (Seraj *et al.*, 2000a; Shevde *et al.*, 2002; Zhang *et al.*, 2006b, 2014b; Hedley *et al.*, 2008a; Smith *et al.*, 2009; Nagji *et al.*, 2010; Ponnusamy *et al.*, 2012; Guo *et al.*, 2015; Kong *et al.*, 2015). Similarly, genetic mapping in mice shows that metastatic potential is

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linked to allelic variations of syntenic regions encoding *Brms1* (Devilee *et al.*, 1991; Hampton *et al.*, 1994a, 1994b, 1996), but *Brms1* does not fulfill genetic criteria as a metastasis modifier locus in the latter studies. Nonetheless, ubiquitous transgenic overexpression of *Brms1* in F_1 generation MMTV-PyMT crosses significantly reduced lung metastases while not affecting primary tumor development (Cook *et al.*, 2012). Surprisingly, selective expression of *Brms1* in mammary tissue under control of MMTV did not block lung metastasis. Knockout of *Brms1* was embryonically lethal.

Higher BRMS1 expression is correlated with decreased metastasis, motility, invasion, resistance to anoikis, ultrastructure, and cytoskeletal organization (reviewed in Welch, 2016). Collectively, all those data suggest that lower BRMS1 expression may have clinical prognostic utility. Studies in histologic samples are limited, but some recent data suggest that BRMS1 expression may predict higher survival in patients with osteosarcoma (Li *et al.*, 2018b). More extensive studies will be required to establish whether BRMS1 is a useful biomarker. While most clinical data corroborate its functional role as a metastasis suppressor, some studies show that BRMS1 expression does not change (Kelly *et al.*, 2005) or expression directly correlates with malignancy (Hicks *et al.*, 2006; Lombardi *et al.*, 2006; Cui *et al.*, 2012). Lack of correlation could be for several reasons, including that RNA and protein levels for BRMS1 do not directly correlate (Hurst *et al.*, 2008, 2009c, 2013). Also, most of the transcriptomic studies do not adequately account for contributions of stromal cells present within the samples. Unfortunately, the quality of reagents, particularly antibodies, has slowed work to understand BRMS1 expression and function. Of note, some commercial antibodies sold as recognizing BRMS1 actually recognize BRMS1L, a related molecule. We, in collaboration with MaryAnn Accavitti-Loper, generated and validated two monoclonal antibodies (IgG isotype (3a1.21) that recognizes the N-terminal region of BRMS1 and IgM isotype (1a5.7) that recognizes the C-terminal region) detect and immunoprecipitate BRMS1 (Hurst *et al.*, 2006, 2008, 2009c, 2009d, 2013; Welch, 2016). Using PCR-based methods, Lianidou *et al.* have shown that lower BRMS1 in circulating tumor cells or cell-free DNA in liquid biopsy specimens are associated with improved outcomes (Ntzifa *et al.*, 2021, 2024). In related studies, they have shown that methylation status of BRMS1 DNA is also a clinically useful biomarker (Chimonidou *et al.*, 2011, 2013a, 2013b, 2017; Ntzifa *et al.*, 2021, 2024). Therefore, BRMS1 expression and regulation have potential to be prognostic biomarkers, but the realization of clinical utility will require fully validated reagents and a deeper understanding of BRMS1 mechanism of action.

Aside from confusion related to reagents, ascribing a particular mechanism of action for BRMS1 has been challenging because of its ability to partially inhibit multiple steps in the metastatic cascade (Welch et al. 2016). Depending on the assay and cell lines used, BRMS1 can inhibit invasion (Shevde *et al.*, 2002; Zhang *et al.*, 2006a; Smith *et al.*, 2009), migration (Zhang *et al.*, 2006a; Smith *et al.*, 2009), adhesion (Zhang *et al.*, 2006a; Phadke *et al.*, 2008; Hedley *et al.*, 2008a; Khotskaya *et al.*, 2014), colonization (Phadke *et al.*, 2008; Hedley *et al.*, 2008a, 2008b), and promote apoptosis (Phadke *et al.*, 2008; Hedley *et al.*, 2008a, 2008b; You *et al.*, 2015). All of these steps involve interactions with the environment, suggesting that a common mechanism would involve response(s) to external signals. The first reported phenotype associated with tumor–microenvironment interaction by BRMS1 was restoration of homotypic GJIC (gap junctional intercellular communication) (Saunders *et al.*, 2000). Similarly, BRMS1 was shown to restore heterotypic GJIC between breast carcinoma cells and osteoblasts (Kapoor *et al.*, 2004).

Other signaling pathways have been implicated and demonstrate a much more complex relationship with BRMS1 expression. Harihar and colleagues were the first to show that phosphoinositide signaling pathways are downregulated by BRMS1. It does so by selectively downregulating phosphoinositol 4-phosphate 5-kinase expression. This downregulation reduces phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2) without changing levels of PtdIns(4)P and PtdIns(3)P (DeWald *et al.*, 2005; Vaidya *et al.*, 2008). PI3K signaling is a key molecule associated with neoplastic transformation and metastasis (Thorpe *et al.*, 2015; Hoxhaj and Manning, 2020; Llorente *et al.*, 2025). However, other molecules implicated in these studies play key roles in lipid raft and primary cilia formation as well as signaling through these structures.

Vaidya *et al.* extended those data, demonstrating that BRMS1 selectively altered signaling in response to different growth stimulatory or inhibitory molecules that can be found in different tissues. Briefly, cells expressing BRMS1 respond differently to epidermal growth factor (EGF), hepatocyte growth factor (HGF), or platelet-derived growth factor (PDGF). The responses varied by whether BRMS1 changed phosphoinositide signaling, whether receptor expression was reduced, or whether other signaling was altered (Vaidya *et al.*, 2008). Of note, Bodenstine *et al.* (2010) showed that the GJIC changes were more closely associated with changes in protein kinase A (PKA) activity.

The variety of mechanisms involved led to a deeper analysis of BRMS1 functions through interacting proteins. BRMS1 is the founding member of a family molecules associated with transcriptional regulation and epigenetics. The family is defined by a conserved region known as the Sds3-like domain, but whether the Sds3 domain is required for BRMS1 function is still uncertain. Critically, BRMS1 itself does not function as a transcription factor. The BRMS1 family includes BRMS1, BRMS1-like (BRMS1L), and SUDS3 (suppressor of defective silencing 3, also known as SAP45 or mSds3) and all three molecules interact with HDAC1. BRMS1 amino acid sequence is 23% identical and 49% similar to SUDS3 and is 57% identical and 79% similar to BRMS1L. BRMS1L (p40) is a component of SIN3–HDAC (switch-independent 3-histone deacetylase) complexes and has been associated with other epigenetic interactomes.

Most of the understanding BRMS1 mechanism of action comes from studies of homologous molecules in other species. Co-immunoprecipitation shows that SUDS3 is integral to formation of orthologous SIN3–HDAC chromatin remodeling complexes in multiple species (yeast, murine, human). The yeast ortholog of SUDS3 promotes Sin3 complex integrity and is essential for histone deacetylase (HDAC) activity. In mammalian cells, SUDS3 is essential for embryonic development and has been implicated in some cancers. However, expression of SUDS3 in metastatic breast cancer cell lines does not suppress metastasis (Silveira *et al.*, 2009), indicating that family members have distinct functions and are not functionally complementary. To elucidate BRMS1's function, it is also important to understand SIN3 complex components and some of their functions. SIN3A and SIN3B are not functionally redundant. SIN3A suppresses metastasis, while SIN3B promotes metastasis (Lewis *et al.*, 2016). SIN3A maintains cellular pluripotency, while SIN3B does not (Saunders *et al.*, 2017). Knockout of SIN3A is early embryonic lethal, while SIN3B lethality is later (Cowley *et al.*, 2005; David *et al.*, 2008). BRMS1 appears to interact with SIN3A (Zimmermann *et al.*, 2021) and SIN3B (Le Guezennec *et al.*, 2006) and has an E3 ubiquitin ligase function on the histone acetyl transferase p300 (Liu *et al.*, 2013).

BRMS1 protein is a 246 amino acid polypeptide and is predicted to be 28.5 kDa, though BRMS1 migrates closer to 35 kDa on SDS-

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PAGE. This may be due to charges in the glutamic acid-rich N-terminal region (aa1–50). *BRMS1* encodes two coiled-coil regions (aa51–81 and aa147–180) and two predicted nuclear localization sequences (NLS, aa198–205 and aa239–245). The proximal NLS, but not the distal NLS, is required for localization to the nucleus (Hurst *et al.*, 2013). However, the so-called second NLS is required for metastasis suppression (Hurst *et al.*, 2013).

The N terminus of BRMS1 has been crystalized (Rivera *et al.*, 2010; Spinola-Amilibia *et al.*, 2011) and its three-dimensional structure determined. However, aside from aa51–98, the structure of full-length BRMS1 has not yet been solved nor has it been crystallized. But a more informative observation was made during those studies – the C terminus of the BRMS1 protein is critical for metastatic suppression (Hurst *et al.*, 2013). Of note, a serine residue immediately upstream of the critical metastasis suppressor domain was shown to be phosphorylated by cyclin-dependent kinase 2 (CDK2) (Roesley *et al.*, 2016). Mutational analysis of S237 ($BRMS1^{S237D}$ (phosphorylation-mimic); $BRMS1^{S237A}$ (unable to be phosphorylated); $BRMS1^{1–229}$ (deletes critical C-terminal domain); $BRMS1^{230–246}$ (C-terminal domain with S237 in the center)) altered BRMS1 interactions with approximately 1200 proteins (Zimmermann *et al.*, 2021). Regardless of whether S237 was mutated to aspartic acid or alanine, BRMS1 protein stability was uncompromised. Likewise, the phosphorylation state (or phosphomimic state) of BRMS1 did cause altered expression of presumptive downstream mediators of BRMS1 (Zimmermann *et al.*, 2021). Paradoxically, impact on in vitro assay results were not consistent with metastasis inhibitory effects of BRMS1. Experimental metastasis assays with MDA-MB-231 cells expressing $BRMS1^{WT}$, S237A, or S237D showed that $BRMS1^{WT}$ and S237D were significantly lower compared to vector control cells. S237A metastasis was not. In fact, S237D had significantly fewer lung metastases than $BRMS1^{WT}$ or S237A. Thus, the inability of BRMS1 to be phosphorylated at S237 does impact metastasis suppressor function. Moreover, the greater ability of S237D to suppress metastasis suggests that BRMS1 phosphorylation status is critically important.

The story of BRMS1 functionality and interaction is further complicated by differential associations with other members of the SIN3–HDAC complexes, when comparing SIN3A complexes in untransformed MCF10A versus metastatic MDA-MB-231 breast carcinoma cells. Of all the interactions, only BRMS1 did not interact with SIN3A in metastatic cells while still interacting with BRMS1L, suggesting that interactions with BRMS1 and BRMS1L differ depending on the transformation state of the cells (Zimmermann *et al.*, 2021). Deeper analysis suggests a complex relationship between BRMS1, BRMS1L, SIN3A, and SIN3B interactions; however, how those interactions lead to different epigenetic regulatory pathways remains to be determined. BRMS1 direct interactions with ARID4A or SUDS3 are not essential for metastasis suppression (Hurst *et al.*, 2008). BRMS1 has two coiled-coil regions (Hurst and Welch, 2011b) and other protein domains that appear to be responsible for individual protein interactions (Seraj *et al.*, 2000c; Hurst *et al.*, 2008, 2009d, 2013). Mutational analysis has unraveled BRMS1 interactions that presumptively regulate metastasis.

BRMS1-interacting proteins have been identified by yeast two-hybrid (Y2H), co-immunoprecipitation (coIP), fluorescence resonance energy transfer (FRET), and mass spectroscopy. In addition to SIN3–HDAC complexes, BRMS1 interactors include chaperone proteins HSP90, HSP70, and MRJ (Hurst *et al.*, 2006), subcellular localization/protein transport by sorting nexin 6 (SNX6) (Rivera *et al.*, 2010) and karyopherin α5 (KPNA5) (Hurst *et al.*, 2006), transcription factors N-myc interactor (NMI) and TAFII250 (Hurst *et al.*, 2006), stress fiber smoothelin (SMTN) (Hurst *et al.*, 2006), chromatin complex SWI/SNF member BAF57 (Hurst *et al.*, 2006), class II HDACs, HDAC4, 5, and 6 (Hurst *et al.*, 2006), AT-rich interacting domain 4A (ARID4A, previously known as retinoblastoma binding protein 1, RBP1 or RBBP1) and SUDS3 (Meehan *et al.*, 2004), ING1 (Nikolaev *et al.*, 2004; Doyon *et al.*, 2006), ING2 (Doyon *et al.*, 2006; Smith *et al.*, 2010), and SAP25 (Shiio *et al.*, 2006).

As with other metastasis suppressors, BRMS1 point mutations are not commonly found in metastatic cells. Diminished expression can occur by loss of heterozygosity, as described earlier. But differential regulation has been demonstrated by multiple mechanisms including promoter methylation (Metge *et al.*, 2008, 2010; Nagji *et al.*, 2010; Chimonidou *et al.*, 2011, 2013a, 2013b, 2017; Yang *et al.*, 2011; Balgkouranidou *et al.*, 2014; Kong *et al.*, 2015; Wang *et al.*, 2015; Xing *et al.*, 2015; Panagopoulou *et al.*, 2017; Xia *et al.*, 2017; Ntzifa *et al.*, 2021, 2024), noncoding RNA regulation of transcription or translation (Sun *et al.*, 2017; Cao *et al.*, 2018; Li *et al.*, 2018b; Farokhimanesh *et al.*, 2021; Gao *et al.*, 2022), protein stability (Liu *et al.*, 2013; Dou *et al.*, 2019; Zhou *et al.*, 2020), and alternative splicing (Chakrabarti *et al.*, 2003; Hurst *et al.*, 2009c; Wu *et al.*, 2013).

The complex saga of BRMS1 highlights difficulties associated with understanding the regulation of metastasis. Even relatively well-characterized epigenetic complexes and pathways, like SIN3–HDAC, are not robustly understood. The megadalton size and mix-and-match composition of the complexes in different cells (and probably under different contexts of those same cells) means that dissecting mechanisms of action will require more cell models, more in vitro models mimicking steps of the metastatic cascade which incorporate all of the relevant cell types and matrices of various tumor microenvironments, and more in vivo assays that recapitulate all of (or most of) the metastatic cascade. Even those considerations do not yet take into account identifying the kinases (if there are others besides cdk2) and phosphatases regulating BRMS1 phosphorylation status or the post-translational modifications of BRMS1 interactors.

LSD1/KDM1A

Histone lysine demethylase 1 (LSD1), encoded by the *KDM1A* gene, was first discovered in 2004 and its discovery contributed to demonstrating histone methylation as a dynamic, not static, process (Shi *et al.*, 2004, 2005). LSD1 is a positive regulator of EMT in gastric and breast cancers (Feng *et al.*, 2016; Zhang *et al.*, 2019). It was first shown that LSD1 regulates the E-cadherin promoter and represses expression by demethylating H3K4me2 in gastric cancer (Zhang *et al.*, 2019). The mechanism of regulation was defined by demonstrating that LSD1 phosphorylation at S112 by PKC is imperative for its ability to demethylate the E-cadherin promoter as a contributor to EMT (Feng *et al.*, 2016). Mutation to a phosphomimetic S112D enhanced metastasis of MDA-MB-231 cells, while phosphodead S112A exerted no effect. This observation was further demonstrated in an ovarian cancer model, where LSD1 overexpression induced expression of EMT markers N-cadherin, vimentin, and MMP2 to enhance migratory phenotypes (Feng *et al.*, 2016; Li *et al.*, 2016d, 2025b). LSD1 enhanced transcription of RNF135 which promoted lung cancer metastasis to the brain in vivo by permitting cancer stem cell self-renewal (Qu *et al.*, 2024). Another target of LSD1 is SEPT6, which promotes the SMAD pathway in NSCLC cells to drive invasion in vitro (Hong *et al.*, 2022). LSD1 can coregulate ERα in gastric cancers to promote gene

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expression of the migratory proteins TSPAN4 and NDST1 (Kang *et al.*, 2025). LSD1 also interacts with RBBP7 to promote expression of genes involved with stemness in breast cancer: SOX9, SOX2, OCT4, and CCND1 (Xi *et al.*, 2025). Recently, it was shown that LSD1 regulates immune evasion in metastatic lung cancer via upregulating expression of PD-L1 (He *et al.*, 2023a).

While LSD1 promotes tumorigenicity and metastasis, there is also evidence of it acting as a metastasis suppressor. LSD1 expression negatively correlates with TGFβ expression and inhibits invasion and metastasis of breast cancer (Wang *et al.*, 2009). LSD1 suppresses migration and invasion of androgen-independent prostate cancer via reduced expression of the focal adhesion adaptor protein, paxillin, and G-protein-coupled receptor, LPAR6 (Ketscher *et al.*, 2014). In turn, LPAR6 overexpression enhances spontaneous metastases from orthotopically implanted tumors. Another study showed that LSD1 loss enhances MMTV-PyMT spontaneous lung metastases due to the enhanced E3-ubiquitin ligase, *TRIM37*, and transcription factor, *ELF3* expression (Hu *et al.*, 2019). The metastasis suppressive effects are not all cancer cell autonomous. LSD1 regulates exosome contents from tumor cells that travel to premetastatic niches through molecular alterations (Liu *et al.*, 2024b; Yao *et al.*, 2024). Exosomes from wild-type and LSD1-knockdown MCF7 breast cancer cells were introduced to mice prior to tail vein injection of wild-type cells which developed more bone metastases (Liu *et al.*, 2024a). The authors found that LSD1 abrogation reduced expression of hnRNPA2B1 via reduced H3K9me2 demethylation to alter microRNA secretion and premetastatic niche remodeling. Similarly, exosomes from MCF7 cells which had lower LSD1 expression impaired endothelial barriers at lung, liver, and brain (Yao *et al.*, 2024).

An additional signaling component downregulated by LSD1 is PIK3IP1, an inhibitor of PI3K/AKT. As a result, downregulation or inhibition of LSD1 enhances expression of PIK3IP1 with concomitant reduction in PI3K/AKT activation in TNBC cells and a corresponding inhibition of metastasis (Li *et al.*, 2025b). Multiple LSD1 inhibitors have been enrolled in a variety of clinical trials (Noce *et al.*, 2023). Domatinostat® is a dual inhibitor of HDAC and LSD1 and has been tested in clinical trials of melanoma and Merkel cell carcinoma (NCT04133948, NCT04393753, NCT03278665). Domatinostat® was effective at reducing expression of multiple genes associated with migration and reduced outgrowth of 4T1 breast cancer cells in lungs of syngeneic mice (Zylla *et al.*, 2022).

LSD1 also interacts with BRMS1 to form a complex regulating expression of multiple genes associated with cancer metastasis (Qiu *et al.*, 2018). Perhaps this provides evidence of a context that may be required to demonstrate tumor suppressive actions of LSD1, where BRMS1 may be necessary to push it in the antimetastatic direction. Since both molecules regulate epigenetics, their respective activities may be determined by site-specific or context-specific complex formation.

Heterochromatin-associated protein 1 (HP1)

HP1 is another example of epigenetics as key to tumor and metastasis regulation. Readers are referred to several excellent reviews (Dialynas *et al.*, 2008; Vad-Nielsen and Nielsen, 2015; Jeon *et al.*, 2022). HP1 was first discovered in *Drosophila* as a nonhistone chromosomal protein, but several paralogs have been identified in multiple species. In humans, HP1 proteins exist in multiple isoforms and splice variants (HP1α/HP1β/sHP1γ) which vary in size from 173 to 240 amino acids. HP1α (Norwood *et al.*, 2004; Lieberthal *et al.*, 2009; Lomberk *et al.*, 2012; Chen *et al.*, 2015; Pongas *et al.*, 2017; Dutta *et al.*, 2020) and HP1β (Nishimura *et al.*, 2006; Tell *et al.*, 2011; Yi *et al.*, 2014; Yang *et al.*, 2015) predominantly, but not always, act as metastasis suppressors by maintaining heterochromatin and repressing invasion-associated genes such as various MMP in several cancers; HP1γ more frequently supports tumor progression, proliferation, and migration in several solid tumors (Takanashi *et al.*, 2009; Slezak *et al.*, 2013; Yi *et al.*, 2014; Alam *et al.*, 2018; Chen *et al.*, 2018b; Eriksson *et al.*, 2018; Okamoto *et al.*, 2019; Zhao *et al.*, 2019b). However, HP1 effects are not limited to solid tumors. Terminally differentiated leukocytes exhibit greatly reduced HP1α/β/γ levels and increased MNEI, whereas 'blast-crisis' leukemia cells show elevated HP1 levels, reflecting distinct heterochromatin states. Elevated HP1 in less differentiated leukemia cells likely supports survival and proliferation, while its repression is associated with terminal differentiation and loss of malignant potential (Popova *et al.*, 2006). There are context-dependent roles where HP1 depletion can not only increase genomic instability and apoptosis but also derepress proinvasive transcriptional programs, emphasizing isoform- and tissue-specific effects on apoptotic evasion and metastasis (Dialynas *et al.*, 2008; Vad-Nielsen and Nielsen, 2015).

As highlighted by other molecules, HP1 effects are tissue and interactor specific. Some of the effects are mediated through metabolism (Okamoto *et al.*, 2019), DNA damage, and/or other stress responses (Lee *et al.*, 2013). One mechanism of regulation of HP1α is via the epigenetic regulator BRD4. BRD4 mediates DNA damage response while repressing HP1α expression (Pongas *et al.*, 2017). siRNA treatment against BRD4 increased HP1α levels and sensitized cells to CHK1 inhibition.

Importantly, as with most or all epigenetic mechanisms, the effects are specific in which transcriptional control is affected (i.e., not genome-wide). However, the epigenetic modifiers can regulate cassettes of genes or operons. These effects are determined by interacting protein complexes analogous to what was described for BRMS1. Some examples include: CRL4B, a ubiquitin ligase, forms a complex with SUV39H1, HP1 (all isoforms), and DNMT3A to establish H3K9 and DNA methylation at tumor suppressor loci, leading to stable silencing. This epigenetic repression is suspected to support cancer cell survival, proliferation, and potentially EMT/invasion, as multiple silenced targets involved in cell adhesion and apoptosis pathways (Yang *et al.*, 2015). HP1γ is required for Myc to regulate miR-451a, an inhibitor of migration in PRAD (Babapoor *et al.*, 2014), thereby promoting cell proliferation and progression. Inhibition of Myc-induced apoptosis was rescued by HP1γ introduction, indicating a protumor, potentially prometastatic role for HP1γ (Chang *et al.*, 2018). All HP1 isoforms were shown to modulate androgen receptor (AR) transcriptional activity, thereby affecting proliferation and survival. Differential regulation of AR by HP1α/β/γ may influence progression to more aggressive, potentially metastatic disease states by altering expression of AR target genes (Itsumi *et al.*, 2013).

Metastasis-associated protein 1 (MTA-1)

MTA-1 was first identified in a panel of rat mammary adenocarcinomas by comparing expression in subclones of low and high metastatic potential (Toh *et al.*, 1994; Toh and Nicolson, 2009). Transfection resulted in increased metastasis in multiple cell lines of different origin. Silencing MTA-1 in prostate cancer cells reduced bone metastasis formation in intracardiac xenografts and impaired tumor growth, indicating its role in supporting metastatic colonization and invasiveness (Kumar *et al.*, 2003). Moreover, CRISPR/Cas9-

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mediated knockout of MTA-1 in human NSCLC cells significantly reduced lung metastatic nodules in nude mice, indicating that MTA-1 promotes colonization and outgrowth at distant sites (Wang *et al.*, 2022). The proposed mechanism by which MTA-1 promotes metastasis depends on the contexts of which pathway is engaged, tropisms for different tissues, and which step in the metastatic cascade is affected (Steeg and Zhou, 1998; Cao *et al.*, 2017a, 2017b; Zhang *et al.*, 2018, 2021b, 2024; Zhou *et al.*, 2026a).

MTA-1 was the founding member of a family of metastasis-associated molecules (Harris and Best, 1988; Li *et al.*, 2009, 2010, 2012a) which frequently function as prometastatic transcriptional coregulators and chromatin modifiers with numerous downstream interactors (Matsuoka *et al.*, 1995, 1996, 2001; Moseley and Nurse, 2010; Yan *et al.*, 2012a, 2023; Sen *et al.*, 2014). Cellular localization is critical to MTA-1 function (Nawa *et al.*, 2000; Talukder *et al.*, 2000; Talukder *et al.*, 2003). Taken together, the prometastatic functions MTA-1 and related molecules are the result of complex epigenetic regulation of multiple steps in the metastatic cascade. Nonetheless, some investigators are exploring MTA-1 as a therapeutic target (Pulaganti *et al.*, 2025).

Formin-binding protein 1 (FNBP1)

Formin-binding protein 1 (FNBP1, also known as FBP17) was first described in an acute myelogenous leukemia yeast two-hybrid screen as altered due to fusion with MLL (*Kmt2a*, a histone methyltransferase) which interacts with the endosomal transport protein SNX2 (Fuchs *et al.*, 2001). FNBP1 also bound tankyrase, which plays roles in both telomere maintenance and cytoskeletal structure in its mutated fusion form and endogenous, wild-type form (Fuchs *et al.*, 2003). FNBP1 is also involved in tubule formation through an interaction with dynamin (Kamioka *et al.*, 2004). Collectively, FNBP1 is involved in multiple processes that could alter metastatic actions of cells by affecting membrane tension and motility (Zegers and Friedl, 2015).

Invasive BRCA exhibits high expression of FNBP1 which drives poor differentiation and invadopodia structural maintenance and generation (Suman *et al.*, 2018). Overexpression of FNBP1 in STAD cells induced actin movement, and silencing of FNBP1 inhibited invasiveness in vitro (Yoon *et al.*, 2021). Likewise, FNBP1 is correlated with invasiveness of bladder cancer (Alessandri *et al.*, 1999).

The mechanism of FNBP1 as a metastasis promoter was largely undefined until recently. FNBP1 is post-transcriptionally regulated by insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) to stabilize the transcript in GBM (Zhang *et al.*, 2025a). Translated FNBP1 then interacts with LASP1 to promote SMAD3-driven glycolysis, providing ATP for motility. FNBP1 also interacts with FAK to promote cell adhesion, migration, and AKT-mediated cell survival in HeLa cells (Zhang *et al.*, 2023a).

LINC00987 can inhibit the interaction of miR-376a-5p with *FNBP1* mRNA, enabling its expression to drive invasion and migration in osteosarcoma cells (Cao *et al.*, 2021a). Wild-type p53 is a potential suppressor of FNBP1 transcription, inhibiting invasion that is lost in p53 double knockout (Suman *et al.*, 2022). Although p53 regulates a plethora of genes, attributing its effects on the invasive phenotype to p53-FNBP1 interactions will require further investigation.

RNA and protein translational control

Another level of epigenetic modification is related to protein translation. Shevde-Samant recently showed that a ribosomal RNA-modifying protein could alter post-transcriptional modifications influencing translation efficiency (Elhamamsy *et al.*, 2026). A multi-omic screen of multiple datasets revealed transcriptional dysregulation in TNBC. The tRNA methyltransferase activator subunit 11-2 (TRMT112) knockdown in TNBC cells significantly reduced proliferation, migration, invasion, and metastasis, while overexpression enhanced tumorigenicity. Analysis of translation revealed increases of prometastatic and stromal remodeling pathways and suppression of immune-related processes.

Their findings are more recent evidence complementing previously reported translational elongation association with metastatic progression (Bjornsti and Houghton, 2004; Mamane *et al.*, 2004). Specifically, higher expression of elongation initiation factor 4e (eIF4E) appears to selectively regulate translation of highly structured and capped mRNA (Zimmer and Graff, 2002; DeBenedetti and Graff, 2004; Mahe *et al.*, 2024; Dang *et al.*, 2025; Fang *et al.*, 2025). Ultimately, eIF4E expression is directly correlated with progression in multiple tumor types.

CEBPδ and NFκB

CEBPδ is a transcription factor implicated in numerous biological processes (e.g., cell differentiation, motility, proliferation, cell death). As with most transcription factors, function is determined by cell type and cellular context, some of which have opposing outcomes (Balamurugan and Sterneck, 2013). For purposes of this review, we will focus on the roles of CEBPδ in metastasis-associated phenotypes. Of note, Esta Sterneck *et al.* have demonstrated a prometastatic function of CEBPδ (Balamurugan *et al.*, 2023). Their results highlighted a critical aspect of interpreting expression data - mRNA and protein expression of E-cadherin do not correlate in the metastases. Using inflammatory BRCA in a three-dimensional culture system, protein stability of E-cadherin, β-catenin, and p120 catenin are promoted through a CEBPδ–COX2–PGE2–GSK3β pathway, in which GSK3β is inhibited. Key to these observations is a mechanism in which CEBPδ contributes to maintenance of E-cadherin expression throughout the metastatic cascade as opposed to the canonical EMT-MET plasticity mechanism (Dongre *et al.*, 2017; Dongre and Weinberg, 2019; Allgayer *et al.*, 2025).

Nuclear factor kappa B (NFκB) was discovered because of its interaction with a sequence in the immunoglobulin light-chain enhancer of B cells. It is widely expressed and is responsible for numerous cellular responses to stress and plays key roles in regulating immune responses. NFκB regulates a number of molecules at the intersection migration, inflammation, and autophagy (Bharti and Aggarwal, 2002; Sun and Xiao, 2003; Wu and Zhou, 2009, 2010), all metastasis-associated phenotypes. NFκ activation generally increases metastasis, largely by promoting EMT, invasion, and survival of tumor cells (Xia *et al.*, 2014; Mirzaei *et al.*, 2022). However, its expression is associated with regulation of other metastasis-associated genes as well (Teng *et al.*, 2014; Cho *et al.*, 2015b; Soror *et al.*, 2024). Recent evidence shows that mtDNA in the extracellular space could be transferred to subsets of myeloid-derived suppressor cells via cGAS-STING-NFκB signaling to promote tumor progression (Lai *et al.*, 2025).

RRM1

Ribonucleotide reductase M1 is an essential component of DNA synthesis and repair by catalyzing production of deoxyribonucleotides and is implicated in NSCLC and PDAC (Brissenden *et al.*, 1988; Wright *et al.*, 1990; Han *et al.*, 2018; Zhu *et al.*, 2018). RRM1

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was first investigated in cancer due to its chromosomal location (11p15.5) near multiple metastasis suppressor genes (Bepler *et al.*, 1999, 2005; Pitterle *et al.*, 1999). However, RRM1 displays both tumor suppressor and promoting functions (Jordheim *et al.*, 2011).

In LUAD (Gautam *et al.*, 2003) and COAD (Qi *et al.*, 2015), RRM1 drives expression of the tumor suppressor PTEN (Phosphatase and Tensin Homolog) to suppress migration, invasion, and metastasis via regulation of FAK. In papillary versus undifferentiated THCA subtypes, differential migratory and invasive phenotypes were observed (Fang *et al.*, 2016). Overexpression enhanced proliferative capacity of both subtypes, but RRM1 enhanced migration and invasion in differentiated cells while inhibiting undifferentiated cells.

Because of its role in DNA repair, RRM1 can be a driver of treatment resistance that induces DNA damage. Overexpression of RRM1 was associated with shorter survival in patients with metastatic BLCA who received gemcitabine as part of their treatment regimen (Matsumura *et al.*, 2017). NSCLC patients with lower levels of other DNA repair genes (*ERCC1*, *BRCA1*, *GSTP1*, but not *RRM1*) exhibited higher metastasis-free survival rates (Tsyganov *et al.*, 2020).

A clinical trial assessing efficacy of a tailored, personalized treatment of NSCLC based on expression of DNA repair/synthesis proteins (RRM1, ERCC1, TUBB3, TYMS, TOP1, TOP2a, BRCA1, and GSTP1) found that classical chemotherapy (vinorelbine/carboplatin) increased the risk of fatality but not metastasis (Tsyganov *et al.*, 2020). In a profiling study, RRM1 was upregulated in SKCM brain metastases as well as other DNA repair genes (Ferguson *et al.*, 2018). RRM1 also appears to drive radioresistance due to its role in DNA repair and through promoting expression of the DNA repair protein RAD51AP1 (Yang *et al.*, 2024). Expectedly, inhibition of RRM1 and RRM2 enhanced radiosensitivity of metastatic neuroendocrine pancreatic cancer (Chow *et al.*, 2024). In contrast, patients with malignant mesothelioma having high RRM1 expression had extended progression-free survival (PFS) in response to combination gemcitabine and cisplatin (Munoz-Montano *et al.*, 2021). Whether this is a cancer intrinsic feature or due to resistance of the immune compartment (or other aspect of the TME) to cytotoxic stress that drives this phenotype would be an appropriate future investigation.

The importance of RRM1 as a prognostic factor in cancer progression remains murky. But it is still logical to hypothesize that increased expression of DNA repair proteins would promote cell survival in response to DNA damaging agents and potentially metastases. There is a relative void in basic research of RRM1 in metastatic progression, and whether it is a critical component or bystander to cancer evasion of cell death.

Noncoding RNA (ncRNA)

Throughout this review, several ncRNA have been mentioned as regulators of metastasis-promoting or metastasis-inhibiting genes. We termed microRNA that regulate metastasis metastamiR (Hurst *et al.*, 2009a,b). The number of metastamiR has been growing (nearly 20,000 publications currently found in PubMed searching the terms 'microRNA AND metastasis') and the mechanisms of action vary greatly (Kim *et al.*, 2018b; Sell *et al.*, 2023). Rather than detailing a list of proposed mechanisms for each, a curated list of metastamiR are listed in Table 1.

Cautions related to ascribing mechanisms to metastamiR include frequent clustering of miRNA which sometimes function like operons, being coordinately regulated and sometimes cross-regulating. Likewise, Rigoutsos *et al.* have demonstrated several miRNA isomers, termed isomiR (Loher *et al.*, 2021; Cherlin *et al.*, 2024). Many studies of miRNA assume that the ends are precisely defined, but they can vary by 2–5 nucleotides, which would change interactions and corresponding mechanisms of action.

Table 1. Select microRNA with functional data regulating invasion and/or metastasis

Name	Effect on invasion or metastasis	Reference
miR-10b	Increase	Ma (2010) and Ma *et al.* (2007)
miR-9	Increase Decrease	Chen *et al.* (2012a), Khew-Goodall and Goodall (2010), Song *et al.* (2014), Sun *et al.* (2013b), Lu *et al.* (2014) and Zheng *et al.* (2013)
miR-96	Increase	Soror *et al.* (2024) and Zhang *et al.* (2015)
miR-182	Increase	Lei *et al.* (2014b), Qiu *et al.* (2014), Sachdeva *et al.* (2014), Segura *et al.* (2009) and Zheng *et al.* (2020)
miR-183	Increase	Davenport *et al.* (2022)
miR-335	Decrease	Chen *et al.* (2019), Hashemi *et al.* (2019) and Tavazoie *et al.* (2008)
miR-126	Decrease	Zhang *et al.* (2013)
miR-148a	Increase	Cai *et al.* (2018)
miR-146a	Decrease	Edmonds *et al.* (2009) and Hurst *et al.* (2009a,b)
miR-205	Decrease	Gregory *et al.* (2008) and Luo *et al.* (2013a)
miR-423	Increase	Sun *et al.* (2017)

Additional classes of ncRNA have since been identified: long ncRNA (lncRNA (Liu *et al.*, 2021)), circular RNA (circRNA), yRNA, arcRNA, and PIWI interacting RNA (piRNA). Each has been implicated in regulating different steps of the metastatic cascade. Multiple mechanisms of action have been associated with various lncRNA: altering EMT, changing immune polarization, TGFβ signaling, NFκB signaling, epigenetic complex expression and formation, and competing endogenous RNA (ceRNA). ceRNA is a recently described hypothesis, whereby RNA transcripts compete with shared pool(s) of miRNA for post-transcriptional control (Kartha and Subramanian, 2014; Tan and Marques, 2014; Tay *et al.*, 2014). An increasing number of lncRNA regulate metastasis-associated phenotypes by regulating miRNA. A curated list is shown in Table 2.

Additionally, other ncRNA are emerging as critical regulators of tumor formation, progression, and metastasis. These include tRNA fragments and rRNA fragments, which are nonrandom cleavage products of the parent molecules that have both intra- and extracellular mechanisms of action (Schimmel, 2018; Cherlin *et al.*, 2020; Panstruga and Spanu, 2024; Pliatsika *et al.*, 2024; Bakowska-Zywicka *et al.*, 2025; Dong *et al.*, 2025; Guan *et al.*, 2025). Even mRNA fragments have been isolated and confirmed to encode microproteins or micropeptides (Aoyama and Storz, 2023; Hofman *et al.*, 2025; Zhang *et al.*, 2025b, 2025c). Perhaps, even the prespliced or intron components are more biologically active than currently acknowledged. Regardless, there is a rapidly expanding role for noncoding RNA in the regulation of cancer and metastasis.

Genetic background and metastasis

Kent Hunter and colleagues used meiotic screens involving genetically engineered mice that develop aggressive mammary cancers to

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Table 2. Select lncRNA with functional data regulating invasion and/or metastasis

lncRNA	Effect on invasion/ metastasis	ceRNA association	Reference
ATB	Increase	miR-200	Shi *et al.* (2015), Wu *et al.* (2021c) and Yuan *et al.* (2014)
BCAR	Increase		Xing *et al.* (2014)
BMOR	Increase		Liu *et al.* (2022)
BREA2	Increase		Zhang *et al.* (2023c)
CCAT2	Increase		Redis *et al.* (2016)
FTX	Decrease	miR-374a	Liu *et al.* (2016)
GAL	Increase		Li *et al.* (2022)
H19 (miR-675)	Increase	miR-138 miR-200a miR-200b/c Let-7b	Luo *et al.* (2013b), Zhou *et al.* (2017), Liang *et al.* (2018), Zhu *et al.* (2014a) and Zhou *et al.* (2017)
H19 (miR-675)	Decrease		Zhu *et al.* (2014a)
HOTAIR	Increase		Kogo *et al.* (2011), Ma *et al.* (2022) and Niinuma *et al.* (2012)
MALAT1	Increase		Arun *et al.* (2016) and Gutschner *et al.* (2013)
MALAT1	Decrease		Kim *et al.* (2018a)
MELTF-AS1	Decrease		Lu *et al.* (2022)
MFSD4-AS1	Increase		Liu *et al.* (2023a)
NORAD	Increase		Tan *et al.* (2019)
PNUTS	Increase	miR-205	Grelet *et al.* (2017)
PTAR	Increase	miR-101	Liang *et al.* (2018) and Luo *et al.* (2013b)
RAMS11	Increase		Silva-Fisher *et al.* (2020)
ZFAS1	Increase	miR-150	Li *et al.* (2015b)

Table 3. Polymorphic genes that alter metastatic efficiency

Gene	Location/function	Reference
Arap3	Cytoskeleton	Crawford *et al.* (2008)
Arid4b	Nucleus	Winter *et al.* (2012)
Arntl2	Nucleus	Ha *et al.* (2016)
Brd4	Nucleus	Crawford *et al.* (2008)
Cadm1	Plasma membrane	Faraji *et al.* (2012)
Cnot2	RNA degradation	Faraji *et al.* (2014)
Cnot7	RNA degradation	Faraji *et al.* (2016)
Cpsf4	RNA degradation	Ross *et al.* (2024)
Csf1r	Plasma membrane	Crawford *et al.* (2008)
Luc71	Nucleus	Crawford *et al.* (2008)
mir216a/b		Faraji *et al.* (2014)
mir217		Faraji *et al.* (2014)
mir290-3p		Goldberger *et al.* (2013)
mir347a/b		Faraji *et al.* (2014)
Nanos1	RNA degradation	Ross *et al.* (2024)
Ndn	Nucleus	Crawford *et al.* (2008)
Nup210	Nuclear membrane	Amin *et al.* (2021)
Pi16	Secreted	Crawford *et al.* (2008)
Pum2	RNA degradation	Ross *et al.* (2024)
Pvrl1	Plasma membrane	Bai *et al.* (2016)
Resf1	Nucleus	Majocha *et al.* (2024)
Rnaseh2c	Nucleus	Deasy *et al.* (2019)
Rrp1b	Nucleus	Crawford *et al.* (2007)
Sipa1	Cytoskeleton, nucleus	Park *et al.* (2005)
Smarcd1	Nucleus	Ross *et al.* (2024)
Tpx2	Nucleus	Geiger *et al.* (2014)
Zbtb16	Nucleus	Bai *et al.* (2016)

identify metastasis efficiency genes (Lifsted *et al.*, 1998; Winter and Hunter, 2008; Ross *et al.*, 2025). Thus far, they have identified more than 20 polymorphic factors that alter metastasis and have validated them functionally in metastasis assays (Table 3). Analogous studies in prostate cancer models have also identified candidate metastasis susceptibility genes (Ono *et al.*, 2013; Patel *et al.*, 2013; Lee *et al.*, 2015), further supporting the idea that inherited susceptibility to metastasis is a general phenomenon.

Interestingly, many of these molecules can be colocalized in complexes or associated with shared pathways (Kent Hunter, personal communication). Furthermore, many of the pathways and complexes are involved in transcriptional regulation, protein translation and/or stability, or other epigenetic processes. This finding supports the assertion that plasticity is a hallmark of cancer metastasis (Welch and Hurst, 2019). Coupled with accumulating evidence that most of the metastasis-associated genes are not mutated in cancer but have altered expression (Welch *et al.*, 2000; Sleeman and Steeg, 2010; Hunter *et al.*, 2018), strongly suggests that epigenetic plasticity, rather than constitutive (in)activation of genes and pathways, is the primary mechanism for metastatic progression.

Another reason for highlighting the studies of the Hunter lab is their broad applicability. There are literally millions of SNP that have segregated in the human population. Those polymorphisms are responsible for multiple traits, including disease susceptibility. As a result, every human is unique (Durbin *et al.*, 2010). The same mutations on different genetic backgrounds result in distinct phenotypes (Threadgill *et al.*, 1995; Antoniou *et al.*, 2010; Ono *et al.*, 2013; Fontaine and Davis, 2016). Similar observations are found in both mice and humans. Some noncancer examples include cystic fibrosis in which many patients homozygous for the CFTRdF508 mutation exhibit a spectrum of lung disease from near-normal to respiratory failure (Boyle, 2007). Similarly, mutations in SOD1 contribute to amyotrophic lateral sclerosis, but the age of onset and severity varies widely in humans (Kammenga, 2017) and mice (The Jackson Laboratory, 2014).

Cancer's genetic origin is clearly understood and accepted. In addition to the nuclear SNP, there are analogous SNP in mtDNA that define mouse strains (Bussard and Siracusa, 2017; Beadnell *et al.*, 2018; Scheid *et al.*, 2021) just as they can identify clades in humans (Wallace and Torroni, 1992; Wallace, 2018). While there

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has been increasing appreciation for the roles of mitochondria in cancer (Beadnell *et al.*, 2018; Scheid *et al.*, 2019, 2021; Welch *et al.*, 2022; Tang and Yang, 2025; Wei *et al.*, 2025; Balamurugan *et al.*, 2026; Berridge *et al.*, 2026; Bostan *et al.*, 2026; Liang *et al.*, 2026), most efforts to investigate the genetics of cellular functions study only the nuclear genome.

We hypothesized that similar SNP in the mitochondrial genome could play a role in cancer metastasis. This hypothesis was supported by the design of Hunter's experiments in which male MMTV-PyMT mice were crossed with females of the other strains. Since one inherits mitochondrial DNA (mtDNA) maternally, there existed the possibility of mitochondrial QTL.

To test this hypothesis, we generated a panel of mitochondrial-nuclear exchange (MNX) mice in which nuclear DNA (nDNA) is paired with mtDNA from other mouse strains, thereby allowing isolation of mitochondrial genetics as an experimental variable (Fetterman *et al.*, 2013; Welch *et al.*, 2023). Paralleling the Hunter experiment, we crossed nDNA-matched MNX with MMTV-PyMT mice and observed nearly identical results with regard to primary tumor latency, number, and size of metastases (Feeley *et al.*, 2015). Extending those experiments using HER2 as a genetic driver, Brinker *et al.* (2017) observed changes in the same phenotypes, but in a driver-dependent manner. Spontaneous tumor formation and metastasis were also altered in aged mice (Vivian *et al.*, 2018). Effects on metastasis were not solely tumor cell intrinsic, as injection of syngeneic melanoma and mammary carcinoma cells into MNX mice resulted in 50%–90% inhibition of metastasis when mtDNA were derived from C57BL/6J mice and a 300%–500% enhancement of metastasis if mtDNA was C3H/HeN-derived (Brinker *et al.*, 2020).

Since mtDNA does not encode any of the adhesion or invasion genes (as well as other tumorigenicity- or metastasis-associated genes), it was questioned whether mtDNA SNP were associated with nDNA methylation patterns and expression patterns (Vivian *et al.*, 2017). Nonetheless, the hypothesis proved correct and the epigenetic methylation patterns were localized. Subsequent studies show similarly specific alterations of baseline populations (Beadnell *et al.*, 2020), microbiota (Welch Lab, manuscript in preparation), and reactive oxygen species production (Brinker *et al.*, 2020). Somewhat surprisingly, metabolomic analyses did not identify a metabolite correlating with the observed phenotypes (Lab). MNX mice show differences in atherosclerosis, adiposity, and diabetes (Fetterman *et al.*, 2013; Betancourt *et al.*, 2014; Bray and Ballinger, 2017; Dunham-Snary *et al.*, 2018; Kandasamy *et al.*, 2019).

Collectively, these data show four things. First, genetic background is critically important for controlling susceptibility to tumor formation and metastasis efficiency. Second, involvement of many QTL in metastasis, both nuclear and mitochondrial, will complicate studies in cancer and metastasis (Swanton *et al.*, 2024). Third, germline mtDNA SNP contribute to many phenotypes and should not be ignored in the study of metastasis. And fourth, the germline backgrounds represent a context which has been understudied in the context of cancer biology.

Cell surface and adhesion

The plasma membrane is the interface between neoplastic cells and the tumor microenvironment. Cells respond to the numerous soluble molecules in plasma and interstitial fluids, and tension exerted by the ECM via receptors and adhesion molecules. Binding of molecules to the cells initiates a cascade of signals that influence epigenetics, transcription, translation, and organelle modification that determine cell functions. Responses vary by which molecule(s) is bound, the strength of the molecular affinity, presence or absence of cofactors that amplify or mitigate signaling, and the length of interactions. This section focuses on surface molecules that have been implicated in metastasis regulation.

Integrins

Integrins make up a family of divalent-cation-dependent, heterodimeric, transmembrane proteins that comprise both normal and pathological functions regulating cell adhesion and signaling. Integrins are a specific subset of cell adhesion molecules that bind to ECM, separate from immunoglobins, cadherins, and selectins (Kadry and Calderwood, 2020). However, the link between cell–cell adhesion and the metastasis hallmarks of motility and invasion is exemplified here by integrins and later by other adhesion molecules (Welch and Hurst, 2019). Twenty-four known αβ dimers are formed from combinations of 18 α and 8 β subunits; the most promiscuous subunit is β1, dimerizing with 12 different α subunits (α1–11, αV). β2 dimerizes with four different α subunits, while β3 and β7 bind two α subunits – β4, β5, β6, and β8 only operate with one distinct α subunit each (Kadry and Calderwood, 2020).

Extracellular ligands for integrin binding are canonically reported as ECM constituents, such as laminin or collagen, among other dimer-specific ECM entities. These drive 'outside-in' signaling canonically via FAK/SRC, ERK and AKT pathways, while other mechanisms of signaling can occur independent of ligand binding (Hamidi and Ivaska, 2018). Heterodimers exist in three conformational states: bent-closed (inactive), extended-closed (intermediately active), and extended-open (active). These states are dictated by divalent cation availability (Ca^{2+}, Mn^{2+}), dimerization partners, or intracellular binding/signaling mechanisms. Canonically, integrins bind ECM to initiate signaling through FAK/SRC, ERK, or AKT. A key signaling activity of most integrins is via association with focal adhesion kinase (FAK), which is commonly linked to invasion, angiogenesis and metastatic spread (Owens *et al.*, 1995; Zhao and Guan, 2011; Cooper and Giancotti, 2019).

During tumorigenesis and cancer progression, integrin subunit expression and abundance can become altered – ratios of integrins inhibitory to cancer progression versus those permitting progression become disproportionate compared to physiologically normal levels of integrin expression (Hamidi and Ivaska, 2018). In primary tumors, a TCGA study assessed integrin regulation across 32 cancers finding an average of 33.5% of tumors harbored alterations (mutation, amplification, deletion, or a structural variant) of at least one integrin gene (Zou *et al.*, 2024).

Assessment of integrin expression using the Pan-cancer Integrin Explorer (PIExplorer) revealed two downregulated (*ITGA8*, *ITGA*9) or upregulated (*ITGAX*, *ITGB4*) integrins in at least 10 out of 15 cancers with matched normal tissue. ITGA8 was reduced across all cancer except for LIHC (upregulated in tumor) and HNSC (no significant difference, NSD). *ITGA9* was reduced across all cancer types except for HNSC, KIRC, STAD, THCA (NSD) Alternatively, *ITGAX* and *ITGB4* were upregulated in 10 out of 15 cancer types (down in two each).

Unsupervised clustering of expression (transcripts per million, TPM) for each integrin across cancer types grouped *ITGA8*, *ITGA7*, *ITGA10*, *ITGB3*, *ITGA1*, and *ITGA9* as mostly downregulated integrins across cancers tested. Meanwhile, one cluster of integrins (*ITGAD*, *ITGA5*, *ITGB7 ITGAM*, *ITGB2*, *ITGA4*, *ITGAL*) was

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upregulated in a subset of cancers (KIRC, KIRP, KICH, BRCA, PRAD, UCEC) and upregulation of a second cluster (*ITGA2B*, *ITGA3*, *ITGB4*, *ITGB8*, *ITGA2*, *ITGA6)* was specific to other cancers (LIHC, THCA, LUAD, LUSC, COAD/READ, STAD, BLCA, ESCA). Interestingly, head and neck squamous cell carcinoma (HNSC) samples displayed upregulation across both clusters.

Differential clustering was predictive of overall survival, and specific to each cluster, suggesting a role for a coordinated integrin dysregulation in patient outcome. By specifically assessing survival within cancer groups, high ITGB8 status was associated with improved patient outcome KIRC, however, the high expression group was associated with worsened patient outcome in low-grade glioma groups. This further emphasizes the nuance of context specific roles of integrins across different cancer types. Moreover, integrin function is dependent upon each heterodimer, which varies by tumor cell origin and the matrices with which the tumor cells interact (reviewed in Hamidi and Ivaska, 2018; Chastney *et al.*, 2025; Maltseva *et al.*, 2025).

It must be noted that, while transcript levels are changed for many integrins, protein abundance may not be properly reflected by mRNA measurements; for example, ITGB8 is downregulated at the transcriptional level in TCGA BRCA data, but at higher abundance in Clinical Proteomic Tumor Analysis Consortium (CPTAC) proteomics datasets, though the number of samples in CPTAC is drastically reduced compared to TCGA (Maltseva *et al.*, 2025).

More specifically, subsets of integrins are associated with metastasis as recently reviewed by Hamidi and Ivaska (2018). Table 4 summarizes their findings as well as those associated with some large-scale comparisons of metastatic versus nonmetastatic cells (Ghandi *et al.*, 2019; Jin *et al.*, 2020; Zou *et al.*, 2024).

E-cadherin, N-cadherin, and cadherin-11

Groundbreaking efforts by the lab of Masatoshi Takeichi using monoclonal antibodies to disrupt cell–cell connections led to the identification of cadherins, named to reflect their calcium-dependent

Table 4. Integrin association with metastasis (Ghandi *et al.*, 2019; Jin *et al.*, 2020)

Gene	Protein	MetMap 125[a] association[b]	MetMap 500[a] association	MetMap 500 penetrance[c]
ITGA1	CD49a	NSD	NSD	NSD
ITGA2	**CD49b**	(−) Liver	(−) Liver;	(+) Lung
ITGA3	**CD49c**	(−) All; (−) brain; (−) liver; (−) lung	(−) Liver	(−) Bone; (−) brain; (−) liver
ITGA4	**CD49d**	(+) Liver	(+) Brain; (+) kidney; (+) liver	(+) Liver
ITGA5	CD49e	NSD	NSD	NSD
ITGA6	**CD49f**	(+) All; (+) bone; (+) lung	(+) All; (+) brain; (+) bone; (+) kidney; (+) liver; (+) lung	(+) All; (+) brain; (+) bone; (+) kidney; (+) liver; (+) lung
ITGA7	ITGA7	NSD	NSD	NSD
ITGA8	**ITGA8**	(−) All; (−) brain; (−) lung	NSD	NSD
ITGA9	**ITGA9**	(+) All; (+) brain; (+) bone; (+) liver; (+) lung	(+) All; (+) brain; (+) bone; (+) kidney; (+) liver; (+) lung	(+) All; (+) brain; (+) bone; (+) kidney; (+) liver; (+) lung
ITGA10	**ITGA10**	NSD	(+) Kidney, (+) liver, (+) lung	(+) Lung
ITGA11	**ITGA11**	(−) All; (−) bone; (−) liver; (−) lung	(−) All; (−) brain; (−) bone; (−) lung	(−) All; (−) brain; (−) bone; (−) kidney; (−) liver; (−) lung
ITGAD	**CD11D**	(−) Brain; (−) lung	NSD	(−) Lung
ITGAE	CD103	NSD	(+) Liver	(+) Liver
ITGAL	**CD11a**	(−) All	(−) All; (−) kidney; (−) liver; (−) lung	(−) All; (−) lung
ITGAM	CD11b	(−) All; (−) bone; (−) lung	NSD	(−) Brain; (−) bone
ITGAV	**CD51**	(−) All; (−) brain; (−) bone; (−) liver; (−) lung	(−) All; (−) brain; (−) bone; (−) kidney; (−) liver; (−) lung	(−) All; (−) brain; (−) bone; (−) kidney; (−) liver; (−) lung
ITGA2B	**CD41**	(+) Liver	(−) Brain; (−) lung	(−) Lung
ITGAX	CD11c[d]	NSD	NSD	NSD

+/− indicates a significant ($p < 0.05$) positive or negative linear regression correlation between metastatic potential and gene expression of each integrin α gene in those cells at a specific organ, or 'All' which is a compilation of scores across all organs. NSD indicates no significant correlation described across all individual organs assessed, or collectively. Gene names with at least one significant correlation are highlighted in bold.

Some genes assessed by this method display consistency as potential prometastatic genes regardless of tissue (*ITGA6*, *ITGA9*). Some display potential antimetastatic gene expression correlation (*ITGA11*, *ITGAV*). Others have differing observations based on tissue (*ITGA2*, *ITGA2B*).

Note, that in some cases, it requires the aggregation of all metastatic sites ('All') to achieve significance, but correlation to cell arrest in single organs is unachieved, or can differ from MetMap125 to MetMap500.

MetMap125 organs assessed: Bone, brain, liver, lung.

MetMap500 organs assessed: Bone, brain, kidney, liver, lung.

Additional experimental information is listed in the primary manuscript, and the data were accessed and assessed via DepMap Portal. Statistics for significant correlations are included in Supplementary Table 1.

[a]Briefly, the original experiment was to simultaneously inject 125 (MetMap125) or 500 (MetMap500) cell lines intracardially followed by examination of single cells arrested in an organ (caution: presumed to be metastases, but not necessarily the case).

[b]Association is the correlation of cancer cell gene expression (CCLE – cancer cell line encyclopedia) with metastatic potential (calculated proportion of metastatic cells at each metastatic site in referenced experimental models).

[c]Penetrance is the percentage of biological replicates in which the cell line was found in each metastatic site.

[d]https://en.wikipedia.org/wiki/Integrin_alpha_X

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adhesive function (Takeichi, 1988). E-cadherin, encoded by *CDH1* on chromosome 16 in humans or *Cdh1* on chromosome 8 in mice, was the first to be discovered and cloned (Yoshida-Noro *et al.*, 1984) and is classically considered a suppressor of invasion in primary tumors (Rodriguez *et al.*, 2012; Bruner and Derksen, 2018; Kaszak *et al.*, 2020). N-cadherin was the next to be discovered (Hatta and Takeichi, 1986) among Type I classical cadherins, including E-cadherin (denoting expression in epithelial cells), N-cadherin (expression initially observed in neuronal cells), and P-cadherin (placental). Type I classical cadherins share the traits of having five repeated extracellular domains and a single transmembrane domain. N-cadherin is encoded by *CDH2* or *Cdh2* on chromosome 18 in both humans and mice, respectively. In contrast with E-cadherin, considered a facilitator of stable epithelial cohesion, N-cadherin enacts dynamic cell–cell adhesion underpinned by its localization in cellular regions that enable motility such as leading edges or heterotypic junctions (Qi *et al.*, 2005). Together, E-cadherin and N-cadherin are used as defining markers of EMT and its antithesis, MET.

E-cadherin sequesters oncogenic effectors such as β-catenin to the cell membrane, thereby preventing their nuclear translocation and subsequent WNT target gene activation (i.e., oncogenic transcription of *Snail*, *Zeb*, *TWIST*, etc.) while also maintaining Hippo-YAP/TAZ activity for contact inhibition (Lin *et al.* 2023). N-cadherin also interacts with β-catenin, as well as p120-catenin, to stabilize Rac1/Cdc42-driven actin dynamics and enhance FGFR signaling, ultimately activating MAPK/ERK and PI3K/AKT oncogenic signaling (Mrozik *et al.*, 2018). Few cancer types (perhaps hematological malignancies) are unaffected by either E-cadherin or N-cadherin as their switch in expression denotes reprogramming of both cellular adhesion and signaling. During EMT, epithelial cells lose junctional integrity (and E-cadherin expression) and acquire mesenchymal traits (and N-cadherin expression). Both are useful, but not necessarily required, for intravasation, extravasation, and ultimately colonization (Fischer *et al.*, 2015; Jolly *et al.*, 2015, 2017, 2019; Zheng *et al.*, 2015; Zhang and Weinberg, 2018; Dongre and Weinberg, 2019; Brabletz *et al.*, 2021). Multiple layers of regulatory mechanisms including epigenetic and promoter methylation, noncoding RNA, and chromatin remodeling impact expression of E- and N-cadherins throughout the metastatic cascade, and consequently their contributions to the process vary with temporal and microenvironmental context.

Complete, constitutive loss of either *CDH1* or *CDH2* is embryonic lethal, reflecting their critical importance as mediators of cell adhesion and signaling hubs (Larue *et al.*, 1994; Radice *et al.*, 1997a, 1997b). Germline heterozygous loss of E-cadherin is associated with invasive lobular carcinoma in a classic two-hit model of oncogenesis that is screened for more diagnostic than prognostic value (Grabenstetter *et al.*, 2020; Bullock and Brunton, 2025). Germline *CDH1* loss-of-function mutation is also associated with autosomal dominant hereditary diffuse gastric cancer (Guilford *et al.*, 1998, 1999; Blair *et al.*, 2020). Having global physiological relevance in cell adhesion outside the topic of neoplasia, CDH1 variants or risk-modifying SNP also contribute to nonsyndromic cleft lip and/or palate (Frebourg *et al.*, 2006; Vogelaar *et al.*, 2013), a craniofacial development disorder called blepharocheilodontic syndrome (Ghoumid *et al.*, 2017), and inflammatory and barrier-related disorders (Schneider and Kolligs, 2015). Pathogenic variants of *CDH2* have been associated with ACOG syndrome (agenesis of corpus callosum, axon pathfinding, cardiac, ocular, and genital defects) (Accogli *et al.*, 2019), neurodevelopmental and neuropsychiatric disorders (Moya *et al.*, 2013; Halperin *et al.*, 2021), as well as cardiac structural disease (Mayosi *et al.*, 2017; Turkowski *et al.*, 2017), reflecting N-cadherin's crucial roles in neural development.

In keeping with its loss during EMT, E-cadherin initially demonstrated functional roles as a metastasis suppressor. In the absence of *Trp53*, epithelial-specific deletion of *CDH1* permitted mammary tumor development in transgenic mice and metastasis to regional lymph nodes occurred more frequently in mice with homozygous loss of E-cadherin than in heterozygous animals (Derksen *et al.*, 2006). Consistent with this, tumor cells isolated from primary mammary tumors with homozygous floxed *CDH1* and orthotopically transplanted into immunocompromised mice formed metastases at multiple distant sites at significantly higher frequency than cells derived from heterozygous tumors (Derksen *et al.*, 2006). In the MMTV-PyMT mouse mammary cancer model, monoclonal antibodies targeting E-cadherin reduced lung metastasis without affecting primary tumor growth and similar reduction of lung metastases was observed using these antibodies with intravenously injected 4T1 mammary cancer cells (Na *et al.*, 2020). Outside the context of breast cancer, conditional E-cadherin deletion also accelerated tumor progression and metastasis in the 'KP' Kras mutant and p53 null mouse model of lung cancer (Sinkevicius *et al.*, 2018).

On the contrary, E-cadherin may support survival and collective migration in other contexts, thereby acting as a promoter of metastasis (Padmanaban *et al.*, 2019; Rubtsova *et al.*, 2022). shRNA knockdown of E-cadherin in 4T1 cells significantly reduced lung metastasis when introduced intravenously into syngeneic mice (Elisha *et al.*, 2018). It is possible that E-cadherin promotes colonization in the lungs at the MET stage (see also CEBP/δ section). Mammary tumor cells derived from MMTV/neu transgenic mice and sorted based on epithelial versus mesenchymal phenotypes lost E-cadherin expression at the site of orthotopic injection of epithelial-sorted cells but became re-expressed later in metastatic lesions (supposedly a requirement of MET) (Palen *et al.*, 2016). Comparison of E-cadherin-negative cells versus E-cadherin-positive 4T1 mouse mammary cancer cell lines, rates of distant metastasis were not significantly different despite more frequent observation of cell individualization in MMT cells via intravital imaging (Ilina *et al.*, 2018). Similarly, liver metastatic burden following intrasplenic injection was equivalent between *CDH1* null and *CDH1*-intact PAAD cells from KPC transgenic mice (Kaneta *et al.*, 2020).

While functional evidence suggests that E-cadherin's roles (if any, depending on cancer type) in suppressing metastasis by restricting EMT or promoting metastasis during MET may depend on the timing of its expression, most initial in vitro evidence supports the paradigm of E-cadherin as a classic metastasis suppressor. Transfection of E-cadherin into highly invasive cancer cell lines results in loss of invasive and migratory capacity (Vleminckx *et al.*, 1991; Chen *et al.*, 1997; Wong and Gumbiner, 2003). Carcinoma cell lines with reduced E-cadherin at baseline correlated with increased invasiveness (Kinsella *et al.*, 1994). However, the observations of E-cadherin as a metastasis promoter are not without support from in vitro mechanistic studies (Lee *et al.* 2024). Clinically, loss or reduced expression of E-cadherin is indicative of poor prognoses in BRCA (Li *et al.*, 2017b), STAD (Lu *et al.*, 2024), COAD (Chang *et al.*, 2022a), PRAD (Umbas *et al.*, 1994, 1997), BLCA, PAAD (Xie *et al.*, 2017), CESC (Peng *et al.*, 2016), OV (Yu *et al.*, 2017), LUAD (Sulzer *et al.*, 1998), and HNSC (Ren *et al.*, 2016).

N-cadherin, on the other hand, can be a clinical indicator of poor prognosis when highly expressed in BLCA (Abufaraj *et al.*, 2017), OV (Assidi, 2022), and HNSC (Luo *et al.*, 2012). With some

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exceptions, preclinical evidence indicates that N-cadherin expression actively promotes metastatic dissemination across multiple epithelial tumor models by enhancing promigratory and proinvasive signaling pathways; however, its functional impact is context dependent and may differ in tumors of mesenchymal origin. Transfection of N-cadherin into nonmetastatic MCF7 human BRCA cells conferred invasive phenotypes in vitro and the ability to metastasize in immunocompromised mice (Hazan *et al.*, 2000). PyMT mice bred to coexpress N-cadherin in the mammary epithelium generated more than threefold more metastatic foci in the lungs (Hulit *et al.*, 2007). Similar increases in metastatic lesions were observed when expressing N-cadherin in the MMTV-Neu mammary cancer model (Qian *et al.*, 2014). Lineage tracing experiments in immunocompetent mice supported the importance of N-cadherin expression prior to colonization as a promoter of metastasis and noted reduced metastatic lesions following N-cadherin deletion (Li *et al.*, 2001). Similarly, expression of N-cadherin in nonmetastatic PRAD models induced invasion and metastasis that was reversed via monoclonal antibody targeting in xenograft models (Tanaka *et al.*, 2010). N-cadherin expression correlates with enhanced invasion and migration in cell culture assays using mammary cancer cells (Nieman *et al.*, 1999; Chung *et al.*, 2013) and other cancer cell types (Li *et al.*, 2001; Maret *et al.*, 2010; Bremmer *et al.*, 2015). However, in certain contexts, N-cadherin may act as a suppressor of tumor growth. In the KPC model of PAAD, loss of N-cadherin promoted precursor lesion and primary tumor development (Su *et al.*, 2016). As with E-cadherin, the timing of expression and switching of N-cadherin may dictate its roles in cancer.

Categorized as a Type II classical cadherin, cadherin-11 is a transmembrane cell adhesion molecule expressed in mesenchymal cells such as bone marrow stromal cells and osteoblasts, for which it was originally named, 'OB-cadherin' (Okazaki *et al.*, 1994; Kimura *et al.*, 1995). Located on human chromosome 16 (*CDH11*) or mouse chromosome 8 (*Cdh11*), $Cdh11^{-/-}$ mice demonstrate osteopenia and skeletal bone abnormalities (Kawaguchi *et al.*, 2001). Mutations in *CDH11* are associated with craniofacial disorders such as branchio-skeleto-genital syndrome, also known as Elsahy–Waters syndrome (Castori *et al.*, 2018), or Teebi hypertelorism syndrome (Li *et al.*, 2021). Aberrancies of expression or function of cadherin-11 associate with fibrotic and chronic inflammatory conditions (Johnson *et al.*, 1997; Schneider *et al.*, 2012; Noss *et al.*, 2015; Chang *et al.*, 2017; Sfikakis *et al.*, 2017; Bowler *et al.*, 2018; Schroer *et al.*, 2019; Franze *et al.*, 2020; Cao *et al.*, 2021b).

Similar to and somewhat overlapping functionality with N-cadherin, cadherin-11 localizes to the cell membrane at points of cell–cell contact and to focal adhesions where it stabilizes p120 or β-catenin, among others (Langhe *et al.*, 2016). In this way, cadherin-11 and its catenin binding partners relocate to the nucleus to promote cancer cell proliferation and invasion through Wnt signaling (Satriyo *et al.*, 2019; Liu *et al.*, 2023b; Shirai *et al.*, 2024) and perhaps immune cell polarization (Li *et al.*, 2012b). In cultured cancer cells, higher expression of cadherin-11 can correlate with increased invasiveness and migration (Chu *et al.*, 2008; Huang *et al.*, 2010; Berghoff *et al.*, 2015). In immunocompromised mice, PC3 PRAD cells expressing cadherin-11 metastasized to bone following intracardiac injection and metastatic burden was reduced following cadherin-11 knockdown using shRNA (Chu *et al.*, 2008). Similarly, shRNA knockdown if cadherin-11 in human glioma cells decreased migration and inhibited tumor growth in nude mice (Kaur *et al.*, 2012). Human MDA-MB-231 BRCA cells with bone tropism had higher expression of cadherin-11 and increased incidence of bone metastases in nude mice than MDA-MB-231 cells with tropism to brain (Tamura *et al.*, 2008). Unmodified MDA-MB-231 cells introduced subcutaneously grew more slowly in immunocompromised mice when cadherin-11 was silenced via siRNA (Satriyo *et al.*, 2019). Targeting cadherin-11 with monoclonal antibodies similarly reduced metastasis of BRCA cells (Chen *et al.*, 2019). In KPC mice, constitutive knockout of Cdh11 slowed primary PRAD growth, prolonged survival, and modulated the immunologic tumor microenvironment (Peran *et al.*, 2021; Sebastian *et al.*, 2023). Clinically, higher cadherin-11 expression is typically associated with more invasive disease and lower survival in BRCA (Chen *et al.*), oral squamous cell carcinoma (Ma *et al.*, 2018a), or STAD (Mita *et al.*, 2023). However, some contradictory findings have been reported in some cancer types. In HNSCC cell lines transfected with shRNA targeting cadherin-11, knockdown tumors grew faster than their control tumors located on contralateral flanks of the same SCID mice (Carmona *et al.*, 2012). *CDH11* demethylation and ectopic cadherin-11 expression in ESCA, STAD, and COAD cancer cell lines decreased cell proliferation, increased apoptosis, slowed migration (Li *et al.*, 2012b). Similar epigenetic downregulation of cadherin-11 was noted to suppress proliferation, promote apoptosis, and limit colony formation, migration, and invasion of COAD cancer cells (Yuan *et al.*, 2019). Correlating with clinical outcomes, high expression of cadherin-11 in newly established human osteosarcoma cell lines increased survival (Nakajima *et al.*, 2008), but no significant impact of cadherin-11 expression on survival was observed in OV (von Bulow *et al.*, 2015).

Cell–cell adhesion, while clearly involved in many steps of the metastatic cascade, involves multiple different molecules that operate in concert. The strength of those interactions and the associated outside-in signaling is reminiscent of the types of signaling described for integrins. Differential expression is dependent on the embryonic origins of cells as well as what the cells become as differentiated tissues. Since cancer cells can sometimes revert to an incompletely differentiated phenotype (Pierce and Cox, 1978; Pierce and Speers, 1988) or exhibit different degrees of stemness (Mani *et al.*, 2008; Brabletz, 2012; Allgayer *et al.*, 2025), it is perhaps not surprising that the effects on metastasis are context dependent.

KAI1/CD82

KAI1 (Kangai1) was initially identified as a metastasis suppressor using microcell-mediated chromosome transfer and mapped to human chromosome 11p11.2 in rat AT6.1 PRAD (Ichikawa *et al.*, 1992). Re-expression of KAI1 suppresses metastasis in multiple cancer types (reviewed in Liu and Zhang, 2006; Tang *et al.*, 2014b, 2015; Prabhu and Devaraj, 2017; Yan *et al.*, 2021; Du *et al.*, 2022) and its expression in multiple cancer types is associated with improved prognosis and/or metastasis-free survival (Ilhan *et al.*, 2009; Malik *et al.*, 2009; Yan *et al.*, 2021). It is a member of the tetraspanin family of four-pass transmembrane glycoproteins which are involved in organizing membrane microdomains. KAI1 is closely associated with cholesterol and lipid rafts and is ubiquitously expressed in normal tissues. As a result, KAI1 plays important roles in regulating cellular signal transduction and adhesion by associating with multiple integrins (Zheng *et al.* 2025). However, its mechanism of inhibiting metastasis involves modulation of adhesion (Guo *et al.*, 2017b), motility (Dong *et al.*, 1995; Takaoka *et al.*, 1998; Uchida *et al.*, 1999; Jackson *et al.*, 2000; Ruseva *et al.*, 2009; Tsai and Weissman, 2011), EMT (Lee *et al.*, 2017, 2019), autophagy (Wu *et al.*, 2011), angiogenesis (Park *et al.*, 2012; Tang

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et al., 2015), and responses to hypoxia and/or growth factors (Park et al., 2012).

Two aspects of KAI1 which are noteworthy are its regulation by NME1 (You et al., 2016), hypoxia/HIF1α (Kim et al., 2010a; Park et al., 2012), and the existence of alternative splice forms (Wei et al., 2024). Although reported in the literature, differential regulation of metastasis and metastasis-associated phenotypes via these changes has not been extensively studied.

CD44

CD44 was first identified as an 80–95 kDa heavily glycosylated cell surface protein that constituted the antigen for InA and InB blood groups (Spring et al., 1988; Jacobs and Sackstein, 2011). It was later shown that CD44 was expressed in hematopoietic cells as a glycoprotein/L-selectin ligand that allowed cell adherence (Oxley and Sackstein, 1994). CD44 binds to other selectins, mediating adhesion of cancer cells to P-selectin (Alves et al., 2008), L/E selectin (Hanley et al., 2006), but dependence varies with isoform and post-translational modification. Additionally, CD44's extracellular interactions include binding to hyaluronan (Aruffo et al., 1990), fibronectin (Ishii et al., 1993), laminin (Ishii et al., 1993), collagen (Ishii et al., 1993), and fibrin (Alves et al., 2008).

CD44 has been identified as a metastasis promoter across various isoforms with differing functions in the regulation of EMT plasticity, extracellular binding functions, and downstream intracellular signaling (Jacobs and Sackstein, 2011; Hassn Mesrati et al., 2021; Primeaux et al., 2022; Mehner et al., 2024; Shen et al., 2024). It is often thought of as a stem cell marker (Morath et al., 2016) as well. Signaling pathways activated by CD44 ligand binding, or CD44 acting as a cofactor for other receptors include promoting receptor function for ligands HGF, VEGF, FGF, NGF, TGFB, CXCL12, and WNT (Orian-Rousseau et al., 2002; Khan et al., 2005, 2021; Orian-Rousseau and Sleeman, 2014; Morath et al., 2016, 2018; Karamanos et al., 2021; Mehner et al., 2024), all involved in protumorigenic signaling that can be speculated as contributors to metastatic potential.

Overall, CD44 displays high expression in many malignancies and is associated with significantly reduced survival probability in TCGA datasets (GBM, HNSC, LIHC, PAAD, KIRC, KIRP, BLCA) accessed via the Human Protein Atlas (Uhlen et al., 2015). CD44 exists in many isoforms and the contributions of various isoforms in metastatic functions are specific: CD44s affects cell differentiation, adhesion, and intracellular actin signaling (Ponta et al., 1994; Zoller, 1995, 2011; Chen et al., 2018a); CD44v3 is involved in tyrosine kinase signaling (Grimme et al., 1999; Wang et al., 2007; Banky et al., 2012); CD44v6 activates cMET or EGFR driving chemotaxis and invasion (Orian-Rousseau et al., 2002; Bellerby et al., 2016; Matzke-Ogi et al., 2016; Ma et al., 2019); CD44v8-10 is involved in modulating redox states of cells in colonization (Yae et al., 2012). All of these isoforms promote metastasis in multiple cancers. Examples include CD44 knockdown reducing COAD cell migration in a transwell system via Lyn kinase/AKT signaling (Subramaniam et al., 2007) and CD44 negatively regulating mitochondria-mediated apoptosis which, in turn, promotes cell survival (Lakshman et al., 2004).

CD44$^{-/-}$*APC*$^{+/min}$ or *trp53*$^{+/tm1}$ mice have no change in tumor burden but exhibit a lack of osteosarcoma metastases (Weber et al., 2002). Similarly, in a *Nf2*$^{-/-}$ LIHC model, CD44 is essential for integrin B2 upregulation and transendothelial migration but did not affect primary tumor growth (Gerardo-Ramirez et al., 2023). However, in MMTV-PyMT spontaneously metastatic mouse models of breast cancer, there was enhanced susceptibility to lung metastases when crossed with CD44 knockout mice (Lopez et al., 2005), suggesting an antimetastatic role under specific conditions.

As with many metastasis-associated genes, expression of RNA and protein do not always correlate. Regulation of the gene products can change metastatic efficiency. For example, CD44 can be endocytosed and degraded. The chaperone protein PEAR1 can bind CD44 to inhibit degradation. Degradation can promote CD44-mediated metastatic functions by facilitating invasive and migratory processes. Blocking PEAR:CD44 interaction conversely reduces migration and invasion in TNBC (Shen et al., 2024).

ITIH5 and HMP19

Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancer types due to its aggressive nature and difficulty in early diagnosis (Siegel et al., 2017). Kurahara and colleagues performed in vivo siRNA screen to identify suppressors of PDAC metastasis and identified HMP19 (Kurahara et al., 2016) and inter-alpha-trypsin-inhibitor-5 (ITIH5) (Sasaki et al., 2017) as suppressors of PDAC metastasis. In both studies, expressions were anticorrelated with PDAC. We will briefly discuss the functions of both and use them as illustrations regarding challenges associated with ascribing metastasis regulatory functions to them.

HMP19 (also known as NSG2, neuronal vesicle trafficking associated 2) suppressed metastasis but also partially inhibited orthotopic tumor growth in vivo. It also inhibited cellular proliferation, migration, and anchorage-independent growth of PDAC cells in vitro. Some of those changes correlated with inhibition of G1/S transition and nuclear translocation of phospho-ERK1/2. These latter properties are consistent with previously reported vesicular trafficking in Golgi. The only other known function for HMP19 is that it encodes a receptor involved in neurotransmission (Chander et al., 2019). Unfortunately, quality reagents have limited studies into its precise mechanism of action.

ITIH5 (inter-alpha-trypsin-inhibitor-5) is a secreted protein whose loss of expression has been described in many different cancers (Peng et al., 2023b; Kosinski et al., 2024; Subramaniyam and Harihar, 2024; Zhong et al., 2025). It is one of the larger family of ECM molecules with multiple reported functions (Zhong et al., 2025). ITIH5 functions as a tumor suppressor in multiple cancer types (Dotsch et al., 2015; Rose et al., 2017; Daum et al., 2021; Zou et al., 2021; Kosinski et al., 2024; Chen et al., 2024a). Reduced expression is apparently due to promoter hypermethylation (Veeck et al., 2008; Rose et al., 2020). As in PDAC, expression of ITIH5 in BRCA is associated with decreased metastatic efficacy (Rose et al., 2017). In contrast to HMP19, intrasplenic injection of PDAC cells reduced the number and size of liver metastases without a similar reduction of lung metastases (Young et al., 2021). This finding highlights the organotropism of metastasis and how metastasis suppression could be organ selective. This conclusion is somewhat analogous to orthotopic growth of KISS1-expressing cells without growth of the same cells at ectopic sites. The basis for the differences can be due to context, though the precise signals are not yet defined.

Another aspect of ITIH5 studies of note is that prior data of ITIH5 (and family members) indicated that it is a secreted molecule and that it would function by interactions with the ECM (Sanders et al., 1992; Bost et al., 1998; Swiatly et al., 2017; Li et al., 2018c; Zhou et al., 2026b). However, Young et al. found that ITIH5 does not appear to be secreted in extracellular vesicles (Young et al., 2021). Furthermore, expression of secretion-defective ITIH5 could

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also arrest PDAC migration and metastasis. Curiously, ITIH5 expression appears to be lost early in PDAC progression with no further loss in metastases. Nonetheless, higher ITIH5 expression appeared to be associated with improved survival in PDAC patients.

The findings of HMP19 and ITIH5 highlight a few important points. First, the differential effects on metastases in different organs suggest that, as we learn more about the underlying (epi) genetics of metastasis, insights related to organotropism will emerge. Those insights may help future physicians cater treatments to likely sites of metastases rather than subjecting the whole person to toxic agents. Second, the functions of proteins are context specific. Secretion may be required to exert a phenotype in some cell types, while it may not be required in another tissue. This conclusion also highlights dangers in extrapolating findings from one tumor type to another. Third, as with other molecules discussed in this review, the quality of reagents and their validation will prove essential to unambiguous advancement of the field.

Cell adhesion molecule 1 (CADM1)

CADM1 was initially identified as a tumor suppressor in NSCLC cells (Kuramochi *et al.*, 2001) and expression suppressed metastasis to the liver (Yageta *et al.*, 2002). However, loss of CADM1 expression is correlated with lymph node metastasis in nasopharyngeal carcinoma in patient samples (Lung *et al.*, 2006) and loss in primary BRCA tumors is associated with metastatic progression and invasion (Takahashi *et al.*, 2012). CADM1's mixed roles in different cancer types are reviewed in Li *et al.* (2021b). In experimental models where CADM1 expression suppresses metastasis, CADM1 interacts with class-I restricted T-cell adhesion molecule, suggesting a potential mechanism of suppression through increasing immune surveillance (Galibert *et al.*, 2005). This interaction increases IFN-γ resulting in rejection in vivo (Boles *et al.*, 2005; Giangreco *et al.*, 2012). Suppressive effects were lost in nude mice which lack T-cell-mediated immunity (Faraji *et al.*, 2012). Functions are associated with inhibition of Ras-Raf-MEK1/2-ERK1/2 signaling and promotion of cell death, STAT3 signaling (Vallath *et al.*, 2016; Wu *et al.*, 2021b), and JAK/STAT signaling (Vallath *et al.*, 2016).

CADM1 expression is methylation dependent (Kuramochi *et al.*, 1997, 2001; Fukami *et al.*, 2003; Kikuchi *et al.*, 2006; Reamon-Buettner and Borlak, 2008; Takahashi *et al.*, 2012; Wikman *et al.*, 2014) and is regulated by TWIST1 (Hartsough *et al.*, 2019). In SKCM, TWIST1 and EMT are inversely correlated with expression of CADM1 (Hartsough *et al.*, 2019; Li *et al.*, 2021b). These complex patterns of expression, signaling, and regulation are likely explanations for the reported tissue-specific effects.

Keratins

Keratins are a diverse family of intermediate filament proteins in epithelial cells. Heteropolymeric filaments which pair type I and type II molecules are expressed in specific patterns and are associated with stages of cellular differentiation. Therefore, they have been useful in categorizing many cancers. In humans there are 54 different keratin genes. The keratin proteins are important for mechanical stability, motility, and cellular integrity and are also involved in intracellular signaling, stress responses, wound healing and apoptosis (reviewed in Moll *et al.*, 2008). While typically located in the cytoplasm, emerging data suggest that some are located on cell surfaces, and the location suggests alternative functions (Ogunnigbagbe *et al.*, 2022). Of note, keratin intermediate filaments are critical intermediaries in cell motility (Yoon and Leube, 2019). In recent publications, keratins have been associated with acquisition of metastatic capabilities (Huang *et al.*, 2026; Li *et al.*, 2025c). Using a COAD model, Huang *et al.* (2026) found that knockdown of KRT81 using shRNA inhibited proliferation, invasion, and migration via regulation of ezrin/radixin/moesin protein complexes. Although the keratins have long been implicated in motility and invasion, a prometastatic role is only a recent observation. As with other metastasis-associated molecules, the effects are likely to be cellular context dependent.

Claudin-1 and claudin-4

Claudins are a multigene family of integral membrane proteins that regulate ion permeability and barrier function while anchored at tight junctions via four alpha-helical transmembrane domains. Early work characterizing claudin-1 and claudin-4 was accomplished by Shoichiro Tsukita's lab via biochemical fractionation of tight junction-enriched membrane preparations followed by protein sequencing of prominent bands not corresponding to known components such as occludin (Furuse *et al.*, 1998; 2002; Morita *et al.*, 1999; Morohashi *et al.*, 2007). Claudin-1 knockout mice display congenital skin defects and die within one day of birth, while claudin-4 knockout mice are viable to adulthood but have increased susceptibility to epithelial injury, inflammation, or infection in some contexts (Furuse *et al.*, 1998, 2002; Kage *et al.*, 2014). Mutations in claudin-1 are linked to ichthyosis and neonatal sclerosing cholangitis (NISCH syndrome), while mutations in claudin-4 are not associated with classic heritable disease (Baala *et al.*, 2002). The differences are tied directly to the nonredundant, foundational barrier-forming functions of claudin-1 versus the redundant, barrier-modulating and signaling functions of claudin-4. While both are embedded in the plasma membrane at tight junctions, differential roles as structural versus regulatory molecules contribute to their roles in metastasis, in which claudin-1 often behaves as a metastasis suppressor but claudin-4 is frequently protumorigenic; however, numerous exceptions have been demonstrated.

In a retrospective study of 83 BRCA cases, decreased CLDN1 expression correlated with recurrence, shorter disease-free interval, and lymph node metastasis, suggesting that loss of CLDN1 expression is linked to a more aggressive, metastatic phenotype (Morohashi *et al.*, 2007). Lack of membrane claudin-1 expression was associated with lymph node metastasis and significantly worse survival in TNBC (Ma *et al.*, 2014a). High expression of claudin-1 in tumor samples correlated with improved overall survival in LUAD patients and when claudin-1 was overexpressed in the human CL1-5 LUAD cell line, the cells demonstrated reduced migration, invasion, and fewer pulmonary lesions when introduced intravenously into SCID mice (Chao *et al.*, 2009). Human SKCM cells that metastasize to brain in xenograft models had lower expression of claudin-1 than a related cell line with preferential tropism to skin; additional experiments determined that overexpression of claudin-1 in brain-colonizing SKCM cells reduced migration in vitro and improved survival in vivo (Izraely *et al.*, 2015). Using MDA-MB-231 TNBC cells, stable overexpression of claudin-1 reduced migration and aggregation (Geoffroy *et al.*, 2020). However, in different hands reduced migration was observed in MDA-MB-231 cells, as well as in MCF7 cells, following siRNA knockdown of claudin-1 (Zhao *et al.*, 2015; Zhou *et al.*, 2015a).

Further contradictory observations were made in STAD cancers. In patient samples of COAD, claudin-1 expression increased with progressive disease and metastasis (Dhawan *et al.*, 2005). Overexpression of claudin-1 in SW480 human COAD cells derived

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from a primary tumor and having low endogenous claudin-1 expression resulted in increased growth in soft agar, faster developing subcutaneous tumors in nude mice, and the development of liver metastases following intrasplenic injection and splenectomy when the parental SW480 cells failed to metastasize. Conversely, siRNA knockdown of claudin-1 in the SW620 cell line, which was derived from a metastatic lesion from the same patient as SW480 cells, eliminated migration, decreased invasion, slowed primary tumor growth, and reduced liver metastases by half or more after injection into the spleen.

Taken together, claudin-1 appears to serve more as a contextual modifier of metastasis than a universal metastasis suppressor. shRNA-mediated knockdown of CLDN1 in human STAD suppressed migration and invasion in vitro while also delaying primary tumor growth and reducing pulmonary metastasis in immunocompromised mice; overexpression of CLDN1 promoted STAD cell migration and invasion (Huang *et al.*, 2015). It is possible that the resulting effects of high versus low claudin-1 expression on metastasis are specific to the type of cancer involved. Based on expression of CLDN1, impact on survival appears to be specific to the type of cancer in which some tumors correlate with improved survival when claudin-1 gene expression is low (such as READ, or ACC), but others fare better when it is high (CESC, THCA) (Bhat *et al.*, 2020). Mechanistically, claudin-1 is capable of suppressing cell migration via interactions with ZO scaffold proteins, occludin, and stabilize E-cadherin to ultimately preserve epithelial cell–cell adhesion (Li, 2021). Conversely, it may also interact with Src family kinases, PI3K, FAK, and β-catenin to delocalize claudin-1 from the plasma membrane to the nucleus, promote focal adhesion turnover, and permit actin remodeling of migrating cells (Singh *et al.*, 2012). The divergent effects of CLDN1 elevation or suppression in the clinical context or opposing results from experimental overexpression or knockdown in vitro may reflect differences in cellular context, junctional organization, and claudin-1 subcellular localization. In poorly differentiated, junction-deficient cells, overexpression of claudin-1 may restore epithelial cohesion and suppresses motility, whereas in cells retaining partial junctional architecture or hybrid epithelial–mesenchymal states, claudin-1 would support motility such that its knockdown reduces migration.

Similar to claudin-1, claudin-4 may suppress or promote metastasis in cancer-dependent contexts. Overexpression of claudin-4 in the SUIT-2 human PAAD cell line reduced metastasis in nude mice following intravenous injection (Michl *et al.*, 2003). Supporting a role in metastasis suppression in OVCA, shRNA-mediated knockdown of claudin-4 in 2008 cells promoted experimental metastasis and accelerated migration in vitro (Shang *et al.*, 2012). On the other hand, CRISPR/Cas9-mediated knockout of claudin-4 in BRCA lines T47D and MCF7 slowed migration and invasion (Murakami-Nishimagi *et al.*, 2023). Similarly, shRNA knockdown of claudin-4 in MCF7 cells inhibited migration, while overexpression promoted scratch/wound closure (Ma *et al.*, 2015). Clinical outcomes associated with claudin-4 expression also differ by cancer type, where high expression is associated with poorer survival in BRCA, STAD, OVCA, and endometrial cancers but longer survival in PAAD (Konecny *et al.*, 2008; Lanigan *et al.*, 2009; Tsutsumi *et al.*, 2012; Liu *et al.*, 2015; Martin de la Fuente *et al.*, 2018). As with cadherin-1, loss or gain of cadherin-4 does not simply weaken tight junctions; it reprograms how epithelial cells interpret adhesion, polarity, and mechanical cues.

Other claudins may also impact cancer progression, but additional data are needed to elucidate the functional roles of each and determine what dictates whether they function as suppressors or promoters (Tabaries and Siegel, 2017).

Caspase 8

Encoding caspase 8, a cysteine–aspartate protease that initiates extrinsic apoptotic signaling, human *CASP8* is located on chromosome 2, while mouse *Casp8* is on chromosome 1. Caspase 8 was discovered through convergent efforts of apoptosis researchers via cloning or mass spectrometry analysis of molecules that bind FADD (Fas-associated death domain) (Boldin *et al.*, 1996; Muzio *et al.*, 1996). Caspase 8 is the cleaved product of procaspase 8, which exists as an inactive zymogen prior to activation and recruitment to DISC (death-inducing signaling complex), enabling it to cleave downstream executioner caspases and other substrates such as Bid. Germline mutations in *CASP8* cause immunodeficiency with the hallmarks of defective apoptosis and immune activation (Chun *et al.*, 2002; Niemela *et al.*, 2015). Complete knockout of caspase 8 is embryonic lethal but mouse models with lineage-specific loss of caspase 8 replicate aspects of human immune pathology, underscoring its key roles outside of cancer (Salmena and Hakem, 2005). Loss or silencing of caspase 8 in tumor cells allows them to evade death receptor-mediated apoptosis, particularly during anoikis, immune surveillance, and vascular transit (Hopkins-Donaldson *et al.*, 2000, 2003).

By maintaining death receptor-mediated apoptotic competence, caspase 8 suppresses metastasis and opposes the cancer hallmark of resistance to cell death. Restoration of caspase 8 in neuroblastoma cells with low endogenous expression led to suppression of metastasis to bone marrow and lungs of chick embryos (Stupack *et al.*, 2001, 2006). Neural crest lineage-specific knockout of caspase 8 in the Th-MYCN mouse model of neuroblastoma increased metastasis to bone marrow without affecting primary tumor growth (Teitz *et al.*, 2000, 2013). Also, lack of caspase 8 in the RP mouse model of LUSC led to increased liver metastases (Androulidaki *et al.*, 2025). The impact of maintaining extrinsic apoptosis as a suppressive mechanism in metastasis is supported by evidence that TRAIL, which functions upstream of caspase 8 to initiate apoptosis, also demonstrates tumor suppressive and metastasis suppressive roles (Grosse-Wilde and Kemp, 2008; Grosse-Wilde *et al.*, 2008; Johnstone *et al.*, 2008). This was further demonstrated by caspase 8 mutations in HNSC which potentially influenced TRAIL-mediated apoptosis and cytokine activity (Cui *et al.*, 2021). Inactivation by mutation or silencing of caspase 8 is indicative of decreased survival in HNSC (Uzunparmak *et al.*, 2020; Lu *et al.*, 2025b) and LIHC (Peng *et al.*, 2023a).

However, under some contexts such as when apoptosis is defective, caspase-8 paradoxically promotes migration via noncatalytic interactions. Aside from its roles cleaving other caspases, caspase-8 interacts with focal adhesion and early endosome proteins, resulting in integrin and adhesion recycling at the cell surface (Graf *et al.*, 2014). Such nonapoptotic functions of caspase 8 may explain contradictory findings in which caspase 8 appears to instead support metastasis (Mandal *et al.*, 2020). Caspase 8 promoted cell migration in vitro and metastasis in chick embryos when NB7 neuroblastoma cells lacked caspase 3 and were therefore considered nonapoptotic (Barbero *et al.*, 2009). siRNA knockdown of caspase 8 in MDA-MB-231 BRCA cells increased migration and invasion (De Blasio *et al.*, 2016). Finally, elevated expression of caspase 8 correlated with worse survival in ESCA (Chai *et al.*, 2023). Whether canonical apoptotic or noncanonical roles

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predominate during metastasis in specific types of cancer remains to be elucidated.

Deleted in colorectal cancer (DCC)

DCC is a transmembrane receptor for netrin (an axon guidance molecule) that was initially identified as a common loss of heterozygosity event in COAD (Fearon *et al.*, 1990). DCC is a receptor that maintains survival when ligand is bound but promotes apoptosis when in the absence of ligand (Mehlen *et al.*, 1998; Rodrigues *et al.*, 2007; Krimpenfort *et al.*, 2012). Netrin-bound DCC interacts with UNC5 (another netrin receptor) allowing activation of multiple pathways involved in regulating migration and cell death via Src, FAK, Rho/Rac, MAPK, and AKT via several crosstalk mechanisms (reviewed in Gespach, 2012).

DCC shows little to no mRNA expression across most cancers (Bartha and Gyorffy, 2021), though low expression is speculated to not be entirely due to mutation as it is in COAD (Fazeli *et al.*, 1997). Data from DepMap (Ghandi *et al.*, 2019, which characterizes cell lines by RNAseq, suggest that cell lines retaining DCC expression are predominantly Ewing's sarcoma, lung neuroendocrine tumors, and mature B-cell neoplasms.

Genetically engineered mice with both alleles of DCC knocked out were generated by Robert Weinberg's group (Fazeli *et al.*, 1997). They found that, while the pups appeared normal, they would die within 24 hours due to inability to nurse. Heterozygous mice failed to develop tumors and exhibited no effect on polyp formation when crossed with APC^{min} mice. Conditional knockout of DCC in K14-Cre; $Trp53^{flox}$ mice did not affect primary tumor development or survival, but metastases were observed at significantly higher frequency among mice lacking K14-restricted DCC (Krimpenfort *et al.*, 2001, 2012).

Overexpression induced apoptosis in cells in vitro by inducing caspase cleavage (Mehlen *et al.*, 1998; Krimpenfort *et al.*, 2001, 2012; Mehlen and Furne, 2005; Rodrigues *et al.*, 2007). Functionally, mutating the caspase cleavage site leads to inactivation of DCC and inhibition of DCC-mediated apoptosis, which enhanced cancer progression in $APC^{+/1638mut}$ mice (Castets *et al.*, 2011). Protease inhibitor subtilisin treatment in neuroblastoma SHSY5Y was sufficient to reduce protein levels of DCC following transient transfection, as the cells did not express detectable levels of DCC endogenously (Forrest *et al.*, 2016).

Netrin-1, a ligand for DCC, expression has been implicated to be regulated by NFκB signaling, which then inhibits the proapoptotic action of DCC (Paradisi *et al.*, 2008). Recently, a Netrin-targeted antibody completed a Phase I clinical trial (NCT02977195, no results posted) with the hopes of promoting the tumor suppressive effects of DCC. Targeting of Netrin has shown promising preclinical results, inhibiting EMT and metastases in in vivo cutaneous squamous cell carcinoma mouse models (Lengrand *et al.*, 2023). However, bulk RNAseq data from this study show that DCC was not expressed in the cells assessed, and therefore, the antimetastatic effects of targeting Netrin appear to occur via a mechanism independent of DCC. Additionally, knockdown of either Netrin-1 or UNC5B was sufficient to inhibit EMT phenotypes.

The results with DCC highlight not only tissue specificity but also may implicate other aspects of metastasis, such as interactions with neurons. Those aspects of DCC function in metastasis have not been measured to the best of our knowledge. Another aspect of DCC function in tumorigenicity and metastasis relates to its chromosomal location near SMAD4 on chromosome 18q. Detailed analysis of loss has not always excluded loss of nearby loci, limiting definitive ascription of DCC as the critical molecule.

Signal transduction in metastasis

Upon stimulation from extracellular moieties, cells initiate signals that interpret that stimulus. Those signals, like the receptors themselves, are regulated by protein–protein interactions and the strength and length of those interactions (Lin et al., 2022). Likewise, signals are transduced between organelles to the cell surface and extracellular space. Cellular signaling is frequently depicted as a line or wire when, in fact, it is a web of interconnecting wires. The three-dimensional matrix of signals determines cell behavior. Several different signaling molecules are correlated with metastasis efficiency. But, as with all of the molecules described in this review, their impacts depend on cell context and the presence or absence of cofactors.

Stress-activated pathways (p38, MKK4, MKK6, MKK7)

The class of p38 mitogen-activated protein kinases (MAPK) mediate cellular responses to stress, cell proliferation, differentiation, motility, and survival, akin to Jun N-terminal kinase (JNK) signaling (Wagner and Nebreda, 2009). In cancer, p38 and its upstream kinases act primarily as signal integrators that restrain survival and outgrowth at secondary sites. p38-α (MAPK14) is the predominant isoform in most epithelial cancers but three other isoforms, p38-β (MAPK11), p38-γ (MAPK12), and p38-δ (MAPK13) may play related roles (Wagner and Nebreda, 2009). In some cancers, p38 and its upstream activators, the mitogen-activated protein kinase kinases (MKKs), suppress metastasis; however, partial attenuation, rather than complete loss, of these pathways can promote metastatic progression. This reflects their dual roles in tumor suppression and stress tolerance. Intact p38 signaling enforces dormancy of disseminated cells, promotes anoikis and stress-induced apoptosis, limits plasticity, and antagonizes ERK-driven proliferation at secondary sites (del Barco Barrantes and Nebreda, 2012). shRNA knockdown of p38 in 4T1 murine mammary cancer cells increased invasion and migration in vitro and promoted spontaneous metastasis in syngeneic mice (Hong *et al.*, 2011, 2015). Using an intraperitoneal mouse model of OVCA metastasis, inactivation of kinase activity in either MKK4 or MKK6, but not MKK7, increased peritoneal metastases via impaired downstream phosphorylation of p38 (Hickson *et al.*, 2006). Other experiments demonstrated that MKK4, MKK6, or MKK7 function as metastasis suppressors supporting p38 or possibly JNK as having influence over metastasis. Identification of MKK4 and MKK7 as metastasis suppressors via microcell-mediated chromosome transfer and functional validation was performed by Carrie Rinker–Schaeffer's lab (Yoshida *et al.*, 1999; Vander Griend *et al.*, 2005). Re-expression of MKK4 or MKK7 suppressed metastasis without affecting primary tumor growth. On the other hand, constitutive heterozygous loss of p38 conferred resistance to metastasis to lung in experimental metastasis mouse models injecting either B16 and LLC syngeneic cell lines (Matsuo *et al.*, 2006). Other studies demonstrated that p38 knockdown decreased migration and invasion in vitro as well as pulmonary metastasis in vivo (Meng *et al.*, 2011). Similarly, deletion of p38 in PyMT mice reduced lung metastatic burden (Wada *et al.*, 2017). In other BRCA models, metastasis was reduced by p38 inhibition (Suarez-Cuervo *et al.*, 2004). In the context of BRCA, p38 may promote tumor growth and progression by affecting vasculature (Limoge *et al.*, 2017).

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SSeCKS/AKAP12/Gravin

AKAP12 (A kinase anchoring protein 12), SSeCKS (Src suppressed C kinase substrate), or Gravin, was initially identified in a screen investigating potential proteins involved in the autoimmune disease myasthenia gravis (Gordon *et al.*, 1992). AKAP12 (Gravin/SSeCKS) was later reported as a regulator of mitogenic signaling as it was suppressed by Src and Ras signaling (Lin *et al.*, 1996). Since then, it has been consistently described as a suppressor of metastasis, primarily in work from the lab of Irwin Gelman (Gelman, 2014).

AKAP12 is a scaffolding protein for protein kinases A and C (PKA/PKC) (Xia *et al.*, 2001). Early studies of AKAP12 in cancer first marked it as a hotspot deleted gene in PRAD, while expression is maintained in normal prostatic epithelial cells (Xia *et al.*, 2001). To inhibit metastasis, AKAP12 impedes podosome genesis via inhibition of RhoA and Cdc42 in prostate cancer cells (Gelman and Gao, 2006). AKAP12 overexpression significantly but mildly inhibits primary tumor cell growth in nude mice, and cells that eventually grew showed reduced AKAP12 levels (Xia *et al.*, 2001). Lung metastases were dramatically reduced in response to downregulated AKAP12 (using a Tet-on expression system) (Xia *et al.*, 2001).

AKAP12 re-expression in prostate cancer cells was sufficient to impede spontaneous metastases to lung from a subcutaneous site, as well as via an experimental metastasis assay (Su *et al.*, 2006, 2010). Forced VEGF expression could overcome the suppressive effects of AKAP12 which drove an antiangiogenic transcriptional profile through downregulation of osteopontin, tenascin C, angiopoietin, HIF1α, and PDGFRβ (Su *et al.*, 2006, 2010). Gelman and colleagues later developed a genetically engineered *AKAP12*$^{-/-}$ mouse model that developed severe hyperplasia in the prostate (Akakura *et al.*, 2008). Prostate tissue from *AKAP12*$^{-/-}$ mice exhibited elevated AKT activity indicated by phosphorylation at S473, without drastic changes in total AKT levels (Akakura *et al.*, 2008).

Furthermore, AKAP12 inhibited activation of the MAPK pathway in a PKC-dependent manner. PKC binding of AKAP12 attenuates its interaction with RAF and reduces downstream MEK/ERK phosphorylation (Su *et al.*, 2010). Specifically, PKCα and PKCδ were activated in *AKAP12*$^{-/-}$ fibroblasts to inhibit Lats-mediated senescence by PKCδ. PKC interaction with AKAP12 is increased during cell confluency leading to a reduction in PKC activity as a potential mechanism of contact inhibition (Guo *et al.*, 2011). *AKAP12*$^{-/-}$ mice were crossed with prostate-specific *Rb* knockout mice to assess alterations in PRAD development (Ko *et al.*, 2014). These mice displayed increased incidence of prostatic intraepithelial neoplasia, and high rates of metastasis to draining lymph nodes compared to wild-type or *AKAP12*$^{-/-}$ mice. In addition to prostate metaplasia, topical skin carcinogen treatment of *AKAP12*$^{-/-}$ mice drives enhanced induction and progression of squamous cell papillomas (Akakura *et al.*, 2011). The epidermal layers of knockout mice were thicker and displayed a dysplastic phenotype with enhanced abundance of FAK and phosphorylated ERK.

AKAP12 also plays roles in premetastatic niche formation. Wild-type and AKAP12$^{-/-}$ mice injected orthotopically with B16-F10 or SM1WT1 SKCM cells showed no alterations in primary tumor growth but developed more peritoneal metastases (Muramatsu *et al.*, 2017). Peritoneal fibroblasts from the knockout mice exhibited higher levels of CXCL9/10 thought to chemotactically attract cancer cells via the CXCR3 receptor. AKAP12$^{-/-}$ mice were predisposed to enhanced metastatic colonization via the premetastatic niche (Muramatsu *et al.*, 2017, 2018). Lung endothelial cells and fibroblasts of AKAP12$^{-/-}$ mice were altered leading to enhanced adhesion of melanoma cells to endothelium via an upregulation of E-selectin. Correspondingly, AKAP12$^{-/-}$ fibroblasts drove E-selectin increase by promotion of STAT3 mediated secretion of VEGF.

AKAP12 transcription is regulated by Src (hence, the alias Src suppressed C kinase substrate), where v-Src promotes SP1/SP3 binding to the AKAP12 promoter along with the co-transcription factor USF1. Transcription is inhibited via HDAC recruitment (Bu and Gelman, 2007; Bu *et al.*, 2011). Another contributor to Src-mediated repression of *AKAP12* expression, transcription factor II-I (TFII-I), was identified using a ChIP mass spectrometry screen of proteins bound to the AKAP12 proximal promoter sequence (Bu and Gelman, 2007). Src-transformed NIH-3T3 cells exhibited elevated TFII-I phosphorylation at Y248. Mutation of this site failed to suppress oncogenic transformation but was sufficient to enhance the gene expression of *AKAP12* (Bu and Gelman, 2007).

CRMP (collapsin response mediator) proteins

CRMP are a family of five (CRMP1-5) cytosolic phosphoproteins that are involved in semaphorin3A signaling and cytoskeletal structure maintenance (Charrier *et al.*, 2003; Yamashita and Goshima, 2012; Cai *et al.*, 2017). All five are essential for proper neuronal development in mice (Yamashita and Goshima, 2012).

CRMP1 was first suspected of being a suppressor of cancer metastasis when it was found to be downregulated in a screen for gene expression across invasive LUAD cell lines (Shih *et al.*, 2001, 2003). Overexpression in invasive LUAD cell lines reduced filipodia generation and Matrigel-transwell invasion (Shih *et al.*, 2001, 2003). The role of CRMP1 in metastatic PRAD was found to be progressively lower in high-grade cancers (Cai *et al.*, 2017). Silencing of CRMP1 led enhanced metastatic phenotypes characterized by increased migration, greater proliferation, and expression of mesenchymal markers with corresponding reductions in epithelial marker mRNA. Conversely, overexpressing CRMP1 caused the opposite effects, including reduced orthotopic tumor growth. A long form CRMP1 (LCRMP1) is associated with metastasis and poor survival in NSCLC patients, and enhanced invasion in culture (Pan *et al.*, 2011). LCRMP1 opposes the effect of the short, originally identified, form of the protein by stabilizing actin (Pan *et al.*, 2011). This was recapitulated in osteosarcoma cells, where a correlation between LCRMP1 expression and N-cadherin/MMP expression was identified (Hou *et al.*, 2016). Another mechanism of LCRMP1 was increased expression of SERPINE1 and promotion of lung cancer angiogenesis when LCRMP1 was localized in the nucleus (Hsu *et al.*, 2025). This latter mechanism was dependent on p53, and it is unclear if the mutated form commonly found in LUAD would alter these results. The regulation of CRMP1 occurs, in part, through connective tissue growth factor (CTGF), where overexpression promotes CRMP1 protein abundance and reduces LUAD colonization in lungs following tail vein injection into SCID mice, though nothing was mentioned regarding metastasis to other organs (Chang *et al.*, 2004a). Additionally, CRMP1 can be regulated by miR-187 in STAD models, where miR-187 is overexpressed and promotes migration and invasion (Ren *et al.*, 2017).

CRMP2 was reported as a metastasis suppressor, though there are questions since it is described as antitumorigenic and whether the effects are due to the short or long form (CRMP2S CRMP2L, respectively) (Yoneda *et al.*, 2012). CRMP2 was first identified in a secretome proteomic screen of COAD cancer cell line conditioned

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media. Expression was abundant compared to normal cells at the transcript level (Wu *et al.*, 2008).

The mechanism of CRMP2 is complex and uncertain. Phosphorylation of CRMP2L at S522 by GSK3B inhibits migration by binding and sequestering ROCKII (Morgan-Fisher *et al.*, 2013). Phosphorylation status S522 also inhibits p53 expression and promotes evasion of apoptosis in A549 NSCLC cells (Oliemuller *et al.*, 2013). However, dephosphorylation by PTP4A3 at T514 inhibits migratory speed in UVM cells in vitro (Duciel *et al.*, 2019). Mutation of both sites shows that both are critical for interaction and stabilization of RECK via inhibiting Wnt and NFκB signaling in BRCA cells (Lin *et al.*, 2020). Mutation of serine to alanine (i.e., phospho-dead, S522A) enhances migration, invasion, and adhesion in NSCLC cells in vitro, while phospho-mimetic (S522D) inhibits those phenotypes (Morales *et al.*, 2021). In another study CRMP2 (DPYSL2) promoted tumor growth of mesenchymal human breast cancers by reducing STAT3-driven migration and metastasis in NOD-SCID mice via interactions with JAK (Abu Rmaileh *et al.*, 2022). It is unclear whether the latter dichotomy is dependent on EMT state of the cells. Furthermore, CRMP2 transcriptional stability can be antagonized by miR-93, a microRNA that, when overexpressed, promotes migration in wound healing assays of PDAC cells (Vila-Navarro *et al.*, 2020). Another explanation relates to the differing functions of CRMP2 in low versus high glucose/oxygenated environments, where EMT is inhibited by CRMP2 upon metabolic stress. Those conclusions are complicated by reductions in HIF1A and increases in Myc reducing CRMP2A levels (Boukouris *et al.*, 2022). In a related study, inactivation of CRMP2 was observed in hyperglycemic conditions in colorectal cancer in a cell line-dependent manner (Chang *et al.*, 2022b).

Like CRMP2, an early proteomic screen associated downregulation of CRMP4 with advancing stage of PRAD (Gao *et al.*, 2010). As with the other CRMP family members, there is evidence of tumor promoting or inhibiting function: CRMP4 is associated with worse overall survival in PAAD (Hiroshima *et al.*, 2013). In Clinical Proteomic Tumor Analysis Consortium datasets, CRMP4 is significantly upregulated at the protein level compared to normal tissue in PAAD but downregulated in COAD and LUSC (Uhlen *et al.*, 2015; Li *et al.*, 2018a). Some activity is thought to be associated with its ability to sequester RhoA activity (Zhou *et al.*, 2015b; Li *et al.*, 2018a).

The bottom line for CRMP functions is that they are isoform- and splicing dependent (Guo and Xia, 2016), promote methylation that is state dependent (Li *et al.*, 2015a; Gao *et al.*, 2017; Huang *et al.*, 2018), interactor dependent, and they are dependent on the cell type from which the cancers originate.

Gelsolin (GSN)

Fujita *et al.* (1995) first identified a mutant form of GSN, P321H, as a tumor suppressor in Ras-transformed fibroblasts. GSN^{P321H} bound actin monomers better and altered severing and nucleating activities of this actin-binding molecule. In BRCA, recurrent alterations and reduced expression relative to normal tissue have been observed as have mutations and downregulation corresponding to clinicopathological features (Baig *et al.*, 2013). The mechanisms for suppressing tumors are varied. GSN suppresses tumorigenicity in STAD (Yuan *et al.*, 2016) cancer through inhibition of p38 signaling. Other reports show the opposite trend – promotion of growth and invasion through the upregulation of p-AKT and p38 pathways (Huang *et al.*, 2016; Ma *et al.*, 2016; Zhou and He, 2023) or EMT (Zhang *et al.*, 2020e). In LUAD, a TGFβ upregulation of GSN results in a cortical actin-rich dormant state that resists cytotoxic lymphocyte killing (Wang *et al.*, 2024b). Perhaps relatedly, upregulation of another stress response transcription factor, ATF3, in BLCA cells decreased metastatic capacity in vivo (Yuan *et al.*, 2013). ATF3 can upregulate CDC42 and other actin-related pathways (Niu *et al.*, 2025).

The tumor suppressive function is outnumbered by a larger portion of the literature showing GSN as a regulator of metastasis or metastasis-associated phenotypes. GSN was first described as a metastasis suppressor in B16 melanoma cells (Fujita *et al.*, 2001) without markedly altering primary tumor growth. The C-terminal region was required for the antimetastatic effect, implicating specific structural domains in the regulation of motility and invasion. Higher tumor GSN expression correlates with longer metastasis-free survival in ER-positive BRCA patients (Stock *et al.*, 2015). Gelsolin in plasma was reported as elevated in stage IV compared with stage I–III COAD patients (Tsai *et al.*, 2012b). GSN overexpression in COAD cells decreased proliferation and invasive capability in vitro (Li *et al.*, 2016c). GSN and 2′-5′-oligoadenylate synthetase 2 (OAS2) exert opposing effects on COAD dissemination, with each preferentially associated with perineural versus lymphovascular invasion. These genes define distinct invasive routes and microanatomical patterns of spread, refining metastasis risk stratification in COAD and implicating GSN in regulating how and where cancer cells invade and/or metastasize to (Kim *et al.*, 2018c).

In general, the mechanisms of GSN in tumor- and metastasis-suppression appear to be due to interference with actin-mediated cellular processes. However, the effects on invasion and metastasis are histotype dependent. For example, GSN expression in HCC correlates with advanced disease and poor patient survival (Zhang *et al.*, 2020). GSN cooperated with actin-related components to enhance invasive and metastatic capacity via EMT-like changes (Deng *et al.*, 2015; Zhou and He, 2023). Like HCC, PRAD exhibited a prometastatic phenotype associated with gelsolin (Hashimoto *et al.*, 2015). In the latter, neurotensin from neuroendocrine-like cells enhanced invasion.

These examples highlight the importance of GSN-interacting proteins. Villin and GSN mRNA expression in primary breast tumors are associated with nodal metastasis status (Borhan *et al.*, 2021). GSN binds directly with Nm23-H1 to inhibits its actin-severing activity (Marino *et al.*, 2013). GSN overexpression in orthotopic and experimental metastasis BRCA models increased liver metastasis which was ablated by co-overexpression of Nm23-H1. In PAAD cells, GSN interacts with podocalyxin-like protein (PODXL) to enhance actin-dependent invasion (Taniuchi *et al.*, 2016). Disrupting the PODXL–GSN interaction reduced invasive phenotypes. In a BRCA model, GSN interacts with BCL2 to inhibit cell adhesion, spreading, and motility through increased F-actin polymerization (Ke *et al.*, 2010). Those results implicate a non-canonical role of BCL2 in actin dynamics. Also, GSN can interact with Cu^{+2}/Zn^{+2} superoxide dismutase to alter reactive oxygen species (Tochhawng *et al.*, 2016), perhaps another signaling mechanism which needs to be further explored in GSN's role in metastasis.

Another layer of regulation for GSN in tumorigenicity and metastasis relates to its relative abundance in cells, which is regulated, in part, by ubiquitin–proteasome-mediated degradation (Ni *et al.*, 2008). Transcriptional expression appears dependent on Ras-Rac signaling (De Corte *et al.*, 2002). Downstream mediators of GSN, such as miR-654-5p and miR-450b-5p, implicate further layers of GSN function (Zhang *et al.*, 2020b).

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SHP2 (PTPN11)

SHP2 (Src homology region 2 domain-containing phosphatase 2; *Ptpn11* (Protein-tyrosine phosphatase nonreceptor type 11), *Syp*) was discovered by the Tony Pawson's lab in 1993 (Feng *et al.*, 1993). SHP2 is a tyrosine phosphatase that catalytically dephosphorylates phospho-tyrosines to alter signaling, structure, or stability of proteins that it interacts with (Chan *et al.*, 2008; Zhang *et al.*, 2004). In addition to a phosphatase domain, SHP2 also has two SH2 domains, each which interact with intramural binding partners, while only the N-terminal SH2 domain autoinhibits its own catalytic site. Phosphorylation of SHP2 at Y542 and Y580 sterically promote an open, catalytically active conformation.

In most cancers, SHP2 promotes oncogenesis. SHP2 mutations lead to hyperactivation and 'RASopothies' which involve elevated RAS activity (Chan *et al.*, 2008). SHP2's role in cancer is predominantly investigated in the contexts of its role in regulating the activity of mutant KRAS by promoting cycling of GTP by dephosphorylating KRAS at pY32 and pY64 (Dance *et al.*, 2008; Bunda *et al.*, 2015). RAS proteins are mutated in ~25% of cancers, with KRAS composing ~85% of these (Hobbs *et al.*, 2016). Despite the importance of SHP2 in regulating KRAS activity, it is demonstrated that SHP2 has minimal effects on the activity of mutant KRAS, while still exhibiting anticancer effects in mutant KRAS models (Chen *et al.*, 2016b; Fedele *et al.*, 2018, 2021; Ruess *et al.*, 2018; Zhang *et al.*, 2016).

SHP2 also regulates JAK/STAT signaling via dephosphorylation of STAT3, PLC signaling through SH2 domain mediated stabilization, PD-L1/PD-1 in immune response, and is recognized as one of the few mitochondrially located phosphatases implicating an alternative role in metabolism (Hansen *et al.*, 2024; Kan *et al.*, 2024; Bye *et al.*, 2025; Hafner *et al.*, 2026; van Vlimmeren *et al.*, 2026; Chen *et al.*, 2022; Guo *et al.*, 2017a; Lin *et al.*, 1996; Wang *et al.*, 2014a; Wang *et al.*, 2005; Wang *et al.*, 2006).

SHP2 expression, pharmacological inhibition, or point-mutations also implicate SHP2 as a metastasis promoter. In BRCA models, for example, knockdown of SHP2 with shRNA impairs Myc stability and reduces lung metastasis (Amante *et al.*, 2023; Qian *et al.*, 2025a). While metastasis reduction alone did not extend survival following surgical resection, combined inhibition of PI3K and SHP2 inhibition extended mouse survival. SHP099 (SHP2 inhibitor) also prevented experimental lung metastases in a syngeneic model (Chen *et al.*, 2016b; Chen *et al.*, 2020a).

Pharmacologic treatment with SHP2 inhibitors impact signaling pathways, some of which impact immune functions. SHP2 inhibition increased the ratio of M1 (cancer-inhibitory) to M2 (procancer) macrophages in the lung and reduced exhausted T cell phenotypes (TIM3/LAG3 positivity). This was further emphasized as a tumor intrinsic mechanism when doxycycline induced shRNA against SHP2 recapitulated the results of the inhibitor. MHC Class I expression increased in response to TNO155 (a SHP2 inhibitor), permitting T cell mediated killing. SHP2 also promotes prometastatic IL-8 secretion via MAPK pathway facilitation in BRCA (Amante *et al.*, 2022).

SHP2 can promote HER2 expression in HER2+ BRCA, while shRNA knockdown ablates lung metastasis (Matalkah *et al.*, 2016; Zhao *et al.*, 2019a). Another mechanism is that SHP2 promotes FAK-mediated, EGF-stimulated migration in BRCA cells (Hartman *et al.*, 2013) Inhibition of AKT (all isoforms) and mTORC with Omipalisib® or mutant-KRAS mediated AKT activation via SHP2 inhibition (SHP099) alone or in combination reduced wound closure in PAAD cells (Mann *et al.*, 2016; Bye *et al.*, 2025; Smith *et al.*, 2020).

SHP2 biology highlights a theme of this review – context matters. Tissue- or organ-selective knockdown shows remarkably different effects. For example, hepatocyte-specific deletion of SHP2 promotes diethylnitrosamine liver carcinogenesis via upregulation of STAT3 mediated signaling (Bard-Chapeau *et al.*, 2011). Despite this role of SHP2, loss of SHP2 in genetic models of LIHC through expression of *ctnnb1*, *PIK3CA*, or *met* inhibited tumor burden (Liu *et al.*, 2018). In PARD, SHP2 knockdown impairs primary and metastatic tumor growth in vivo (Zhang *et al.*, 2016). SHP2 knockdown inhibits invasion of oral cancer cells in vitro, and in vivo lung metastasis (Wang *et al.*, 2014a). The SHP2 inhibitor hexachlorophene inhibits RAS/MAPK pathway activity and PI3K/AKT pathway activity in LUAD cells, impairing migration and invasion (Fu *et al.*, 2022). Mutant, constitutively active/gain of function SHP2 (E76K) enhances GBM migration and invasion in vitro and in *vivo* through activation of CREB (Yang *et al.*, 2019a).

Likewise, macrophage specific SHP2 knockout promotes COAD liver metastasis in vivo (Wu *et al.*, 2023). This leads to enhanced, prometastatic VEGF, MMP2, and MMP9 production in the liver preparing a premetastatic niche. SHP2's SH2 domains also interact directly with PD-1 at pY223 and pY248 to inhibit T-cell receptor signaling, providing a mechanism of tumor-extrinsic immune evasion in T cells (Peled *et al.*, 2018).

PI3K, AKT pathways

Phosphoinositide 3-kinase (PI3K) defines a family of kinases (Whitman *et al.*, 1985; Toker, 2012) that are activated by multiple mechanism, including integrins, cytokine receptors, receptor tyrosine kinases, G-protein-coupled receptors, and CD19 (Carnero *et al.*, 2008; Liu *et al.*, 2009). The PI3K family contains four classes: Classes IA, IB, II, and III, each of which with distinguishing structures and functions.

PI3K proteins phosphorylate PtdIns (phosphatidylinositols), phosphorylated lipids with a carbohydrate compound (inositol) group, and two fatty acid chains that act as second messengers in signal transduction that lead to AKT activation (reviewed in Carnero *et al.*, 2008; Manning and Toker, 2017; Degan and Gelman, 2021; Liu *et al.*, 2009) (Table 5). Phosphate addition of PtdIns(4,5)P2 (also known as PIP_2) to PtdIns(3,4,5)P3 (PIP_3) recruits PDK1 and AKT to the cell membrane allowing their activation. Phosphatase and tensin homolog (PTEN) is a tumor suppressor commonly mutated or downregulated in cancers; PTEN operates in opposition to PI3K by dephosphorylating PIP_3 to PIP_2 (Cantley and Neel 1999). Activating mutations in PIK3CA are oncogenic through constitutive AKT activation, while mutant RAS promotes both AKT and MAPK pathways (Giehl, 2005; Stephens *et al.*, 2005; Tsilimigras *et al.*, 2018).

AKT is also a family of three kinases (AKT1, AKT2, AKT3); the term 'AKT'; originated from a thymoma producing subset of the mouse strain AKR by multiple researchers at the Rockefeller Institute in the 1930s (Xie and Weiskirchen, 2020). AKT1, 2, and 3 are also known as Protein Kinase B (PKB) α, β, and γ, respectively.

PI3K and AKT are heavily involved in cellular migration through the many pathways it activates in cancer and metastasis. The three AKT isoforms execute their own specific functions and regulatory mechanisms, of which many have been studied in cancer, recently reviewed by Degan and Gelman (2021), Agarwal *et al.*, specifically in the context of COAD metastasis (Agarwal *et al.*, 2017), and Hinz and Jücker in the context of BRCA (Hinz and Jucker 2021). Differences in AKT1 acts opposingly, but in accordance with the narrative of this review, as both metastasis suppressor, but as an oncogene as well (Degan and Gelman, 2021; Hutchinson

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Table 5. PI3K signaling molecules

Class	GeneID	Protein name	Domains	Catalytic action
IA	PIK3CA	p110-α	ABD – RBD – C2 – Helical – Catalytic	PtdIns(4,5)P2 → PtdIns(3,4,5)P3
	PIK3CB	p110-β		
	PIK3CD	p110-δ		
	PIK3R1	p85-α	SH3 – PR – BHD – PR – SH2 – SH2 – SH2	
		p55-α	PR – SH2 – SH2 – SH2	
		p50-α		
	PIK3R2	p85-β	SH3 – PR – BHD – PR – SH2 – SH2 – SH2	
	PIK3R3	p55-γ	PR – SH2 – SH2 – SH2	
IB	PIK3CG	p110-γ	ABD – RBD – C2 – Helical – Catalytic	
	PIK3R5	p101	ABD – Gβγ-BD	
	PIK3R6	p87/p84		
II	PIK3C2A	PIK3C2	PR – CBR – PR – RBD – C2 – Helical – Catalytic – Px – C2	PtdIns(4)P → PtdIns(3,4)P2; PtdIns → PtdIns(3)P
	PIK3C2B	PIK3C2	PR – PR – PR – RBD – C2 – Helical – Catalytic – Px – C2	
	PIK3C2G	PIK3C2	PR – RBD – C2 – Helical – Catalytic – Px – C2	
III	PIK3C3	VPS34	C2 – Helical – Catalytic	PtdIns → PtdIns(3)P
	PIK3R4	VPS15	Catalytic – HEAT – linker region – WD40 repeats	

Table adapted from Liu *et al.* (2009) and Safaroghli-Azar *et al.* (2023).
Abbreviations: ABD, adaptor binding domain; BH3, Bcl2 homology domain 3; C2, membrane binding domain; CBR, clathrin binding region; Gβγ-BD, G-protein coupled receptor binding domain; PR, proline rich; Px, phosphoinositide binding domain; RBD, Ras binding domain; SH, Src homology domain.

et al., 2001; Hutchinson *et al.*, 2004). AKT1 is mostly described as protumorigenic but has roles as an inhibitor of metastasis – while AKT2 is the metastasis promoting isoform (Degan and Gelman, 2021). The three isoforms were first suspected to have separate, independent functions based on the different phenotypes of knockout mice of each gene (Chin and Toker 2009; Degan and Gelman, 2021).

Cantley's group that described PI3K also discovered that AKT activity was regulated by phosphoinositols/PI3K (Franke *et al.*, 1997). They specifically found that PtdIns-3,4-P2 could raise the levels of phosphorylated AKT1, promote AKT dimerization activity, and that mutating the pleckstrin homology domain of AKT failed to elicit increases in AKT activity with phosphatidyl inositol treatment.

Activated AKT is phosphorylated at T308 and S473 (Alessi *et al.*, 1997; Manning and Toker, 2017). AKT is phosphorylated and activated by PI3K mediated conversion of PIP_2s to PIP_3, with PDK1 (*PDPK1*) as an additional regulating kinase. Although other phosphorylations and post-translational modifications can regulate function, T308 and S473 are attributed as the required and rate-limiting sites for AKT activity (Alessi *et al.*, 1997; Manning and Toker, 2017). The predominant components of the PI3K/AKT pathway are enacted when active AKT phosphorylates FOXO proteins, GSK3, TSC2, NFκB, and MDM2 to impede their inhibitory effects on cell survival, proliferation, migration, and metabolism (Agarwal *et al.*, 2013a; Amiri and Richmond, 2005; Manning and Cantley, 2007; Manning and Toker, 2017; Hinz and Jucker 2019; Islam *et al.*, 2023; Qiao *et al.*, 2008). This is not a complete list, as AKT is involved in over 10 major signaling pathways (Qiao *et al.*, 2013) – AKT1 alone was shown to interact with 364 different proteins by an immunoprecipitation–mass spectrometry experiment in *Drosophila* (Vinayagam *et al.*, 2016).

Phosphorylated FOXO transcription factors are sequestered by 14-3-3 proteins in the cytoplasm, preventing the transcription of apoptotic genes (e.g., *FASL*, *TRAIL*, *BIM*, *PUMA*), and cell cycle regulators (*p21*, *p27*) (Brunet *et al.*, 1999; Manning and Toker, 2017). Transcription of glycolysis genes *PEPCK* and *G6PC* are initiated, as well as insulin signaling genes (e.g., *InsR*, *IGF1R*, *IRS2*). GSK3 phosphorylation by AKT was discovered in response to insulin-mediated AKT activation (Cross *et al.*, 1995). AKT and MAPK coordinate to phosphorylate GSK3 and prevent regulation of c-Myc by marking it for degradation (Saksela *et al.*, 1992; Pulverer *et al.*, 1994; Cross *et al.*, 1995). GSK3 inhibition by AKT also promotes β-catenin mediated *Myc* transcription. Inhibition of the TSC2 (tuberous sclerosis complex 2) is a mediator of mTORC (mechanistic target of rapamycin) activation (Inoki *et al.*, 2002). Activated mTORC maintains phosphorylated and active AKT in a positive feedback loop (Sarbassov *et al.*, 2005). AKT catalytically regulates NFκB activity as well, which further promotes angiogenesis, invasion, and apoptosis evasion (Agarwal *et al.*, 2017; Amiri and Richmond, 2005; Hinz and Jucker 2019; Islam *et al.*, 2023; Qiao *et al.*, 2008).

PI3K/AKT/mTORC signaling promotes several mechanisms of survival via metabolism, resistance to therapy, survival, or EMT processes (Chin and Toker 2009; Zhou and Huang, 2011; Degan and Gelman, 2021; Islam *et al.*, 2023; Paskeh *et al.*, 2023; Leiphrakpam *et al.*, 2025). PI3K/AKT signaling as a promoter of metastasis has been extensively reviewed in the context of BRCA/PRAD to bone metastasis (Hinz and Jucker 2021).

Motility, invasion, and metastasis are enhanced by AKT-mediated phosphorylation of vimentin at S39 (Zhu *et al.*, 2011). Oral squamous cell carcinoma cells display reduced EMT marker protein levels, and increased E-cadherin in response to AKT inhibition (Hong *et al.*, 2009). In the absence of Ephrin ligand, AKT promotes migration in glioma and PRAD cells, but Ephrin receptor EphA2 inhibits AKT-mediated migration when stimulated (Miao *et al.*, 2009; Lau *et al.*, 2023). AKT phosphorylation of EphA2 at S897 occurs in the absence of Ephrin ligand. It was later found that

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mutation of this site inhibits recruitment of the GEF (guanine nucleotide exchange factor) Ephexin4, and impairs migration and apoptosis resistance in COAD and PRAD cells (Kawai *et al.*, 2013; Lau *et al.*, 2023). Coordination of AKT/mTORC and MAPK-interacting proteins 1 and 2 (MNK1/2) leads to phosphorylation eukaryotic of initiation factors (eIFs) that promote gene expression of metastasis and migratory genes in several cancers (reviewed in Lineham *et al.*, 2017).

Many inhibitors of AKT (pan-AKT inhibitors) lack specificity to individual isoforms, but some do show differential inhibitory efficacy between isoforms (Degan and Gelman, 2021). Studies using AKT/mTORC inhibitors affect metastatic properties, but it is important to consider isoform specificity. Mechanistic studies have elucidated the effects of specific isoforms in metastasis promotion and suppression. AKT1 activation in PAAD increases IGF-IR expression in a positive feedback loop that leads to activation of AKT2, as well, promoting β1-integrin mediated migration (Chin and Toker 2009; Tanno *et al.*, 2001). PyMT mice with constitutively active AKT1 develop mammary tumors with reduced latency, but no differences in metastasis development compared to AKT-wild-type PyMT mice (Hutchinson *et al.*, 2001). Note: the authors do not specify which AKT isoform; however, Irie and colleagues implicate AKT1 (Irie *et al.*, 2005). Accordingly, overexpression of AKT1 in human BRCA T4-2 cells enhanced in vivo tumor growth, but reduced in vitro migration and invasion (Liu *et al.*, 2006). Among isoforms, AKT1 has the unique capacity to regulate the cytoskeletal protein, Palladin – Palladin phosphorylation by AKT1 acts in an antimigratory fashion (Chin and Toker 2010). AKT1 promotes nuclear factor of activated T cells (NFAT) proteasomal degradation via GSK3 inhibition, preventing promigratory transcriptional activity in BRCA cells (Yoeli-Lerner *et al.*, 2005; Yoeli-Lerner *et al.*, 2009). AKT1 and AKT3 shRNA treatment increases BRCA cell migration, while AKT2 shRNA reduces migration, but only in some contexts (Chin *et al.*, 2014). Other studies of AKT3 knockdown increase migration, but do not change proliferation (Chung *et al.*, 2013). AKT1, but not AKT2/3 phosphorylate the promigratory GTPase αRhoC – inhibition of AKT1 by siRNA actually reduced invasion of BRCA cells with high αRhoC levels, while AKT2/3 had no effect (Lehman *et al.* 2012). αRhoC high BRCA cell invasion was reduced by AKT2 siRNA but not siAKT1. ShRNA against AKT1 also enhanced matrix invasion in vitro (Brolih *et al.*, 2018). AKT1 null TNBC cells also display enhanced migration through Boyden chambers (Kempska *et al.*, 2023).

In OV studies, however, AKT1 silencing reduces migration and invasion (Meng *et al.*, 2006). LIHC studies have demonstrated AKT1 phosphorylation dependent on Leucine-rich repeat-containing 1 (LRCC1) expression promotes VEGF secretion, migration, and invasion (Liu *et al.*, 2025). AKT1 activation in osteosarcoma cells promoted migration and invasion in vitro and lung metastasis in vivo through regulation by miR-19a and RhoB (Zou *et al.*, 2018). Constitutively active AKT1 induction in a non-metastatic MSKC mouse model promoted brain and lung metastasis formation in vivo (Cho *et al.*, 2015a). Similar results were observed in PAAD KrasG12D/+ mice, where constitutively active AKT1 accelerated in vivo metastasis formation (Albury *et al.*, 2015).

Human COAD cells with AKT1 or AKT2 knocked out display reduced clonogenicity and liver metastasis (Ericson *et al.*, 2010). Following up, RNA sequencing revealed specific transcriptional profiles altered by ablation of the separate isoforms (Haggblad Sahlberg *et al.*, 2017). Another COAD study showed no effect of AKT1 knockdown, but AKT2 shRNA inhibited metastasis to the liver (Agarwal *et al.*, 2017). The first study utilized splenic injections, while the second used an orthotopic method. Knockdown versus knockout efficacy, or cell lines used could be a contributing factor in this discrepancy as well. In a neuroblastoma model, siRNAs against AKT1 and 3 failed to alter N-myc protein levels, while AKT2 inhibition suppressed N-myc levels, in vitro migration, and in vivo liver metastasis (Qiao *et al.*, 2013).

It was recently shown that a tamoxifen inducible, systemic AKT1 knockout in *MMTV-ErbB2* mouse model reduced tumor metastasis to the lung compared to AKT1 competent mice (Chen *et al.*, 2020). The authors elegantly demonstrate that systemic AKT1 loss inhibits metastasis via stromal AKT1 mechanisms, specifically lung neutrophil derived angiogenesis to promote extravasation and colonization.

Angiopoietin-1 (Ang-1) is a strong promoter of angiogenesis. Another mechanism by which PI3K/AKT is implicated as a tumor-extrinsic metastasis promoter is by Ang-1 activating endothelial cell PI3K/AKT pathways via the Tie2 receptor, promoting survival of endothelial cells in the TME (Kim *et al.*, 2000). VEGF also promotes endothelial cell survival and sprouting by activating AKT and ERK pathways (Liu *et al.*, 2000). It is specifically the AKT1 isoform that regulates this endothelial cell VEGF-mediated migration in an mTOR dependent fashion (Chen *et al.*, 2005; Phung *et al.*, 2006; Graupera *et al.*, 2008; Davies *et al.*, 2019).

PI3K/AKT activity can be stimulated by a plethora of cytokines, growth factors, cell contact events, or intracellular signaling (Carnero *et al.*, 2008; Liu *et al.*, 2009). Specific evidence of regulating events of AKT activity and outcomes on metastatic behavior have been found, and a few are described here. Inhibition of the TGFβ receptor suppresses AKT phosphorylation in BRCA subcutaneous tumors (Futakuchi *et al.*, 2019). TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) promotes AKT phosphorylation and bone metastasis of BRCA cells (Fritsche *et al.*, 2015). The adipocyte hormone, leptin, can induce AKT activity to promote PAAD migratory activity, and obesity promotes PAAD-liver metastasis in vivo by splenic injection (Mendonsa *et al.*, 2015a). Bone-marrow mesenchymal stem cells conditioned media promotes migration of PRAD cells and AKT phosphorylation (Mognetti *et al.*, 2013). In addition, cancer cell-induced tumor microenvironment acidosis can promote AKT activity driving NFκB activation and expression, inviting metastatic phenotypes of promoting invasion in COAD and BRCA models (Yang *et al.*, 2019b). RUNX2, a metastatic regulator, contributes to AKT activation in several cancers (Cohen-Solal *et al.*, 2015). In PRAD, AKT1 can promote EMT, and is inhibited at the translation level by miR-143-3p (Armstrong *et al.*, 2023).

It is clear that AKT pathways are a nexus between cellular input from the microenvironment. It is also clear that PI3K and AKT pathways intersect with multiple other pathways in which cells respond to signals. Additionally, it is clear that the PI3K and AKT pathways are involved in tumorigenicity and metastasis. What is not so clear is why the roles of these molecules vary so greatly, depending upon context. More research will be required to delineate the roles for specific isoforms in metastatic progression. Defining how each is differentially regulated and development of isoform-specific inhibitors will be critical to addressing these questions.

HUNK (MAK-V)

In vivo evidence indicates that HUNK promotes metastatic progression in breast cancer models. Hunk-deficient tumors had a dramatically reduced incidence of lung metastases, and re-expression of wild-type Hunk (but not kinase-dead Hunk)

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restored metastatic potential in orthotopic transplant models, implicating its kinase activity in metastatic behavior (Wertheim *et al.*, 2009). Subsequent work also demonstrated that HUNK enhances BRCA metastasis in vivo via phosphorylation and stabilization of EGFR, leading to increased EMT, migration, and lung colonization in mouse models (Williams *et al.*, 2020). In contrast, HUNK over-expression reduced migration in vitro and metastasis to regional lymph nodes from orthotopically injected BRCA cells in a doxycycline-inducible model (Quintela-Fandino *et al.*, 2010). The effect was thought to be via inhibition of cofilin and protein phosphatase 2-A (PP2A). HUNK1 also inhibits COAD EMT (Han *et al.*, 2023), suggesting another mechanism by which metastasis is regulated.

NDRG1/Drg1/Cap43/Rit42/RTP/PROXY-1

N-Myc downstream regulated gene-1 (NDRG1) is predominantly described as a tumor suppressor but exhibits well studied functions in a variety of physiological phenomena (Ellen *et al.*, 2008; Melotte *et al.*, 2010; Azad *et al.*, 2025). Several independent studies characterized NDRG1/Drg1/Cap43/Rit42/RTP/PROXY-1 in the 1990s; however, NDRG1 emerged as the official gene symbol HGNC:7679 (You *et al.*, 2022). DRG1 and NDRG1, despite the similarity in name, were first described independently. DRG1 was described as *differentiation related gene-1* in COAD cells as increased during differentiation (van Belzen *et al.*, 1997, 1998) and PRAD cells upregulated by androgen signaling (Mori *et al.*, 2021). Like DRG1, TDD5 was described as an androgen responsive gene in PRAD cells with differential response to testosterone and dihydrotestosterone (Lin and Chang, 1997). Tunicamycin responsive protein (RTP) was described in endothelial cells as induced by tunicamycin, homocysteine, and 2-mercaptoethanol (Kokame *et al.*, 1996). Cap43 was described as a gene whose expression was induced via treatment with nickel compounds (NiCl2, Ni3S2) or okadaic acid which drive increased intracellular calcium levels (Zhou *et al.*, 1998).

NDRG1 functions as both cancer suppressor and promoter. TCGA data show that high expression of NDRG1 correlates with an unfavorable prognosis in BRCA, LIHC and LUAD and glioma while higher expression is associated with favorable prognosis in renal cancers (Uhlen *et al.*, 2017). Many studies have demonstrated an inverse correlation of NDRG1 expression and patient outcome (Strzelczyk *et al.*, 2009; Soror *et al.*, 2024; Wang *et al.*, 2024a). Shortly after its discovery, NDRG1 overexpression was found to inhibit BRCA, LUAD, COAD, and BLCA metastasis in multiple mouse models, while primary tumor outgrowth was relatively unaffected. Metastatic properties (in vitro) or metastatic tumor growth (in vivo) were diminished (Kurdistani *et al.*, 1998; Bandyopadhyay *et al.*, 2003, 2004, 2006; Kovacevic and Richardson, 2006). Overexpression reduced in vitro PAAD invasiveness and angiogenesis via downregulation of IL-8, MMP9, and VEGF suggesting a role for NDRG1 in regulating tumor oxygenation and invasion (Maruyama *et al.*, 2006). In contrast, NDRG1 correlates with poor prognosis and stage in LIHC (Chua *et al.*, 2007; Akiba *et al.*, 2008; Cheng *et al.*, 2011; Wang *et al.*, 2024a), CESC (Nishio *et al.*, 2008), THCA (Gerhard *et al.*, 2010), LUAD (Fan *et al.*, 2012), TNBC (Jadhav *et al.*, 2024), UCEC (Ijichi *et al.*, 2025), and CHOL (Zhang *et al.*, 2012c).

NDRG1 is most extensively studied in neurodegenerative diseases (reviewed in Fang *et al.*, 2014; Joshi *et al.*, 2022; Azad *et al.*, 2025). Notably in Charcot-Marie-Tooth disease, mutations in NDRG1 were studied, but provided no clues regarding its roles in cancer since there is no evidence of those mutations driving cancer incidence (Ellen *et al.*, 2008; Ibanez-Julia *et al.*, 2018). The mechanisms in cancer remain unclear; however, NDRG1 interacts with molecules implicated in EMT and metastasis. NDRG1 interacts with Rab4a to promote recycling of E-cadherin, promoting epithelial phenotypes (Kachhap *et al.*, 2007). Iron chelators can inhibit EMT specifically via upregulation of NDRG1 in metastatic PRAD cells (Chen *et al.*, 2012c). A potential target of NDRG1 is β-catenin (Jin *et al.*, 2014). While promoting β-catenin signaling to inhibit EMT could be antimetastatic in some cancers, driving a potent signaling pathway capable of inducing carcinogenesis in other cancer types (e.g., COAD) would be deleterious. In a proteogenomic screen of COAD metastases to the liver, PIM-kinase promoted liver metastasis via NDRG1 phosphorylation at S330 (Zhao *et al.*, 2026). The mechanism demonstrated in this study showed that NDRG1 acts as a metastasis suppressor and pS330 marks it for degradation via ubiquitination. Additionally, NDRG1 suppresses Wnt signaling to inhibit metastatic phenotypes via EMT regulation (Liu *et al.*, 2012) while it promotes rather than antagonizes EMT in STAD (Ureshino *et al.*, 2012).

Another important point regarding NDRG1 is that its cellular functions are dependent upon cellular localization, which varies by tissue type (Fang *et al.*, 2014). Thus, in addition to cell type, cellular localization is another variable which is understudied for most of the metastasis-associated proteins reviewed here.

OGR1/GPR68

OGR1 (ovarian cancer G-protein-coupled receptor 1) was so named due to its discovery by cloning from an OV cell line in 1996 (Xu and Casey, 1996). OGR1 is a G-protein-coupled receptor that can bind sphingosylphosphocholine (SPC) driving calcium accumulation and/or extracellular acidity to activate inositol phosphate signaling and cAMP accumulation (Xu and Casey, 1996; Liliom *et al.*, 2001; Xu, 2002; Ludwig *et al.*, 2003; Mogi *et al.*, 2005; Tomura *et al.*, 2005a, 2005b). OGR1 (GPR68) is overexpressed in many cancers yet it exhibits both pro- and antitumorigenic or pro- or antimetastatic roles depending upon context (Justus *et al.*, 2024).

OGR1 was first described as a metastasis suppressor in the context of PRAD (Singh *et al.*, 2007). Overexpression failed to alter primary tumor growth, but metastasis development was inhibited in mice. Migration was also inhibited in vitro. In OV cells, OGR1 overexpression inhibited proliferation, adhesion, and migration in vitro by promoting binding to ECM proteins fibronectin, vitronectin, and collagens I and IV (Ren and Zhang, 2011), perhaps by increasing 'stickiness.' In breast cancer cells, OGR1 overexpression drove Rho activation to inhibit Rac1 to diminish cell migration in vitro (Li *et al.*, 2013b).

Subcutaneous injection of PRAD into OGR1$^{-/-}$ mice inhibited tumor outgrowth, but adoptive transfer of myeloid cells from wild-type mice into OGR1$^{-/-}$ mice rescued tumor growth in vivo (Yan *et al.*, 2014). There could be multiple mechanisms supported by data in different cellular contexts. OGR1 is regulated by hypoxia via HIF1α transcription (de Valliere *et al.*, 2016). Overexpression in HNSC is suspected to be due to the hypoxic environment of these tumors (Zhang *et al.*, 2020d). OGR1 is also an essential gene for acidity induced PD-L1 expression in HNSC, potentially being a driver of immune evasion in this context (Mori *et al.*, 2021). Additionally, a recent study showed inhibition of growth in BRCA cells when OGR1 is depleted in vitro and in vivo by inhibiting acid-induced lipid uptake (Pillai *et al.*, 2022). G-protein-coupled

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receptors like OGR1 (GPR4, GPR65, GPR132) that respond to pH are implicated as potential tumor promoters in several cancers (Insel *et al.*, 2020). OGR1/GPR68 inhibition or knockdown can induce apoptosis in a zebrafish xenograft model of GBM via upregulation of intracellular lipid peroxidation (Neitzel *et al.*, 2024).

OGR1 can also drive intracellular calcium signaling necessary for motility of medulloblastoma cells via TRPC4 (calcium channel protein) expression. Whether this change in intracellular calcium signaling is responsible for metastasis modulation is still a matter of conjecture. However, multiple studies have demonstrated roles of calcium in metastasis (Alessandro *et al.*, 1996; McGary *et al.*, 1997; Tsuruo *et al.*, 1985; Welch *et al.*, 1989, 1990b). Certainly, other divalent cations are critical for MMP activities (Nelson *et al.*, 2000; Lynch and Matrisian, 2002) and invasion, making such speculation reasonable.

RECK (reversion-inducing cysteine-rich protein with Kazal motifs)

RECK is a cell surface molecule that is frequently downregulated in many cancer cell types (Takahashi *et al.*, 1998). The original characterization showed that RECK suppresses tumorigenicity by regulating MMP9 via two mechanisms: (1) RECK suppresses MMP-9 secretion, and (2) RECK actively inhibits MMP9 protease activity. RECK is also an interactor with CRMP2 (Lin *et al.*, 2013) and is a ubiquitously evidenced tumor suppressor. A recent study in PAAD demonstrated that combining pancreas-specific ($Ptf1a^{Cre/+}$) RECK knockout with $Kras^{G12D/+}$ led to greater cancer incidence and lowered survival probability while increasing spontaneous liver metastases in this model as well as with an additional p53 heterozygous knockout (Masuda *et al.*, 2023). Reintroduction of RECK expression downregulates multiple EMT genes and increases E-cadherin which results in MET and inhibited metastatic outgrowth. Collectively, RECK is a well characterized metastasis suppressor via inhibition of MMP2/9 and EMT.

In addition to the associations with MMP9 and EMT, we use RECK as an example to highlight upstream regulation of metastasis-associated genes and emphasize how it is critical to consider *pathways* of metastasis regulation rather than simply single molecules. There are several documented methods of oncogenic downregulation of RECK. RECK has been found to be post-transcriptionally regulated by multiple microRNA (Clark *et al.*, 2007; Loayza-Puch *et al.*, 2010; Nagini, 2012; Alexius-Lindgren *et al.*, 2014; Bautista-Sanchez *et al.*, 2020) (Table 6). Further, HDAC inhibitors can prevent epigenetic repression of RECK transcription (Chen *et al.*, 2017). Another evidenced mechanism of transcriptional regulation is via LINC01419, where LINC01419 stabilizes EZH2 RNA driving histone methylation of the RECK promoter (Zhang *et al.*, 2020a). Mutant Ras signaling was shown to drive retinoblastoma binding protein-7 (*RbAp46*) and DNA methyltransferase 3b (*DNMT3b*) expression and downstream suppression of the RECK promoter (Chang *et al.*, 2004b, 2006; Yeh *et al.*, 2015).

Table 6. microRNA negative regulators of suppressor RECK

microRNA name	Associated cancer and reference
miR-15a	Neuroblastoma (Xin *et al.*, 2013)
miR-15b-5p	PRAD (Chen *et al.*, 2018c)
miR-15b/16	BRCA, SKCM, LUAD, COAD, PAAD (Loayza-Puch *et al.*, 2010)
miR-16	ECSC (Zhu *et al.*, 2014b)
miR-21	COAD (Wang *et al.*, 2019) GBM, BRCA, STAD (Shi *et al.*, 2013) LIHC (Zhou *et al.*, 2013) CHOL (Namwat *et al.*, 2012)
miR-25	STAD (Zhao *et al.*, 2014)
miR-30b-3p	Glioma (Jian *et al.*, 2019)
miR-92a	COAD (QD Wei *et al.* 2019b) LUAD (Lin *et al.*, 2013)
miR-92b	LUAD (Lei *et al.*, 2014a)
miR-96	Iseki *et al.* (2018)
miR-135b	LIHC (Li *et al.*, 2015c; Yang and Jiang, 2019)
miR-182	CHOL (Zheng *et al.*, 2020)
miR200b/c	COAD (Pan *et al.*, 2015) BLCA (Cheng *et al.*, 2016)
miR-210	CHOL (Fu *et al.*, 2023)
miR-221	Papillary thyroid carcinoma (Wei *et al.*, 2019c) COAD (Qin and Luo, 2014)
miR-372/373	BRCA, SKCM, Lung, COAD, PAAD (Loayza-Puch *et al.*, 2010)
miR-374b-5p	Xie *et al.* (2014)
miR-375	COAD (Wei *et al.*, 2019a)
miR-590-5p	Oral squamous cell carcinoma (Bao *et al.*, 2021), COAD (CW Kim *et al.*, 2018) STAD (Shen *et al.*, 2016)

MTBP (MDM2-binding protein)

MTBP was first identified in a yeast two-hybrid screen and was validated for binding to MDM2 in mammalian cell lines by immunoprecipitation (Boyd *et al.*, 2000). The authors demonstrated that MTBP transfection was sufficient to inhibit cancer cell line growth via G1 cell cycle arrest, and this could be overcome by overexpression of MDM2. MTBP was subsequently shown to regulate MDM2-mediated p53 degradation (Brady *et al.*, 2005). MTBP also promotes expression of *Myc* transcriptional targets in BRCA, where MTBP expression was higher in patient samples and correlated with impaired survival (Grieb *et al.*, 2014a; Grieb *et al.*, 2014b). MTBP also forms a complex with replication proteins Treslin and TopBP1 which mediates recruitment of PCNA to chromatin during S-phase; this led to longer S-phase due to slower replication when MTBP was silenced (Boos *et al.*, 2013). A study on DNA damage control found that replication fork speed was increased in response to knockdown of MTBP or Treslin to drive induction of DNA damage response pathways which could cause the previously observed increase in S-phase time (Maya-Mendoza *et al.*, 2018).

MTBP has demonstrated both pro and antitumorigenic roles in primary disease, while in metastasis studies, has only been observed as a metastasis suppressor (Li *et al.*, 2025a). Homozygous knockout of MTBP is embryonic lethal in mice (Iwakuma *et al.*, 2008). $MTBP^{+/-}$ mice live longer and have an overall reduced cancer incidence while developing lymphomas (Grieb *et al.*, 2016). Iwakuma *et al.*, demonstrated that heterozygous $MTBP^{+/-}$ mice combined with $p53^{+/-}$ genotype display enhanced development of metastases. Fibroblasts derived from these mice exhibit enhanced migratory capacity in vitro (Iwakuma *et al.*, 2008). In an osteosarcoma model, MTBP inhibited ACTN4-mediated in vitro cell migration and in vivo metastases through downregulating expression of ACTN4

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and directly impeding ACTN4-F-actin bundling (Agarwal *et al.*, 2013b). This was corroborated in a LIHC model but also implicated other factors in MTBP metastasis suppressor function. Supporting this idea, ACTN4 manipulation failed to alter migration in some contexts (Bi *et al.*, 2015). A study in lung cancer showed that LNC-CRYBG3 promotes MDM2 upregulation, and that MDM2 antagonizes MTBP-mediated inhibition of ACTN4, thereby promoting invasion in vitro and in vivo (Wu *et al.*, 2021a). Another mechanism demonstrating metastatic suppression by MTBP shows that MTBP sequesters IPO7 to inhibit pERK translocation to the nucleus, preventing transcription of ELK-1 target genes *EGR1*, *c-fos*, and PKCα (Ranjan *et al.*, 2018). This was further demonstrated in a liver carcinogenesis model where genetically modified mice with reduced expression of *MTBP* displayed worse survival and increased pERK nuclear localization (Ranjan *et al.*, 2023).

In clinical samples, MTBP expression was lost in HNSC and was correlated with reduced survival (Vlatkovic *et al.*, 2011). MTBP expression was reduced in LIHC (Bi *et al.*, 2015) and corresponded with reduced metastases (Ranjan *et al.*, 2018). In COAD, MTBP promotes expression of the EMT transcription factor ZEB2, where knockdown of MTBP reduced migration in a ZEB2 dependent manner (Shayimu *et al.*, 2021).

However, others have shown that MTBP is expressed at a higher level in metastatic LIHC cells (Lu *et al.*, 2015) and STAD (Wang *et al.*, 2017). Human Protein Atlas shows that high expression of MTBP associated with unfavorable prognosis from TCGA data in LUAD and PAAD cancers. In contrast, stratification of high and low expressing patients in HNSC shows higher expressing MTBP patients have improved survival (Uhlen *et al.*, 2017). An important caveat to ascribing MTBP's role in metastasis suggests that p53 mutation status has not been assessed in every study. Since MTBP is an interactor of MDM2, it is unclear whether its role changes based on the context of mutant vs wild-type p53 status.

RKIP (Raf-kinase inhibitor protein)

RKIP (a.k.a., *PEBP1*, Phosphatidylethanolamine Binding Protein) was first discovered simultaneously as a 23 kDa protein in bovine brain and rat spermatozoa (Jones *et al.*, 1983; Bernier and Jolles, 1984; Sedivy, 2011). The first study of RKIP in cancer showed that its localization was excluded from the nucleus in Ha-ras-transformed NIH-3T3 fibroblasts (Satake *et al.*, 1989). RKIP is integrated into multiple signaling pathways. RKIP was speculated to be involved in GTP/GDP binding protein mediated signaling based on studies of a highly conserved protein in other organisms (Banfield *et al.*, 1998). RKIP is indeed a binding partner of RAF as assessed in a yeast two-hybrid screen with RAF-BXB (truncated form of the kinase domain) as bait (Bruder *et al.*, 1992; Yeung *et al.*, 2000). RKIP is a competitive inhibitor of the Raf-1/MEK complex which prevents downstream MAPK/ERK signaling (Yeung *et al.*, 2000). RKIP is regulated by PKC family proteins which phosphorylate S153 which, in turn, disrupts binding to Raf leading to ERK activation in response to EGF (Corbit *et al.*, 2003). Phosphorylation shifts RKIP binding from Raf to G-protein-coupled receptor kinase 2 (GRK-2) leading to GRK-2 phosphorylation of GPCR at inhibitory phosphorylation sites (Lorenz *et al.*, 2003; Lee *et al.*, 2022). This PKC-regulated function of RKIP promotes intracellular cAMP accumulation via B-adrenergic receptor signaling when RKIP is phosphorylated and prevented from exhibiting its inhibitory effects on the MAPK pathway. RKIP also antagonizes NFκB pathways by inhibiting IκB kinase activity following TNF stimulation (Yeung *et al.*, 1999) and regulates Notch1 (Noh *et al.*, 2016), 14-3-3 (Gu *et al.*, 2013), and autophagy (Noh *et al.*, 2016) pathways. Interestingly, the differentiation molecule, SOX2, can be regulated by RKIP (Cho *et al.*, 2022).

RKIP was first described as a metastasis suppressor in PRAD (Fu *et al.*, 2006). Expression is lost or lower in PRAD and, when over-expressed or re-expressed, leads to suppression of metastasis as well as angiogenesis and invasion without altering proliferation rate or soft-agar colony formation in vitro. When $RKIP^{-/-}$ mice were bred to transgenic adenocarcinoma of the mouse prostate (TRAMP) mice, there was reduced tumor latency and enhanced lung metastases (Escara-Wilke *et al.*, 2015). As in PRAD, forced overexpression of RKIP inhibits, while RKIP suppression promotes in vitro cellular migration/invasion of SKCM (Schuierer *et al.*, 2004), LIHC (Lee *et al.*, 2006), and glioma cells (Martinho *et al.*, 2012) (perhaps via upregulation of miR-98 (Chen *et al.*, 2013)).

RKIP is reduced, lost, or associated with poor prognosis in metastases from BRCA (Hagan *et al.*, 2005), SKCM (Schuierer *et al.*, 2004), LIHC (Lee *et al.*, 2006), COAD (Al-Mulla *et al.*, 2006; Minoo *et al.*, 2007; Kim *et al.*, 2015), cutaneous squamous cell carcinoma (Zaravinos *et al.*, 2009), BLCA (Afonso *et al.*, 2013; Zaravinos *et al.*, 2009), PAAD (Kim *et al.*, 2010b; Song *et al.*, 2012), CESC (Hu *et al.*, 2011; Martinho *et al.*, 2013a), STAD (Jia *et al.*, 2012), ESCA (Birner *et al.*, 2012; Guo *et al.*, 2012), NSCLC (Yan *et al.*, 2012b; Wang *et al.*, 2014b), nasopharyngeal carcinoma (He *et al.*, 2015; Yi *et al.*, 2016), and GBM (Gimenez *et al.*, 2015). Accordingly, higher expression of RKIP correlated with extended survival in glioma patients (Maresch *et al.*, 2011). In some cases, lower expression in primary tumors was prognostic for poorer survival and metastasis development. In contrast, RKIP is a significant prognostic marker for metastatic progression in PRAD (Fu *et al.*, 2006), COAD (Al-Mulla *et al.*, 2006; Doyle *et al.*, 2013; Zlobec *et al.*, 2008), and STAD (Li *et al.*, 2014; Martinho *et al.*, 2013b).

It is important to emphasize that measurement of RKIP expression, like for many signaling molecules, provides an incomplete story. RKIP in its phosphorylated, inactive form, is present in multiple myeloma (Baritaki *et al.*, 2011; Shvartsur *et al.*, 2017). Later studies showed that pS153 RKIP correlated with survival in NSCLC (Huerta-Yepez *et al.*, 2011), as well as in SKCM (Cardile *et al.*, 2013), COAD (Cross-Knorr *et al.*, 2013), BRCA (Al-Mulla *et al.*, 2013), and nasopharyngeal carcinoma (Li *et al.*, 2016b).

In addition to its roles in metastasis, RKIP is implicated in other cancer-associated phenotypes. RKIP is a critical regulator of drug resistance, where overexpression in DNA-damage resistant BRCA and PRAD cells promotes apoptosis in response to DNA-damage inducing drugs or radiation (Chatterjee *et al.*, 2004; Odabaei *et al.*, 2004; Woods Ignatoski *et al.*, 2008). In a similar manner, Rituximab (CD20 monoclonal antibody) treatment of non-Hodgkin's B-cell lymphoma cells upregulates RKIP expression sensitizing the cancer cells to chemotherapy-induced apoptosis. BCL-XL is repressed by RKIP inhibition of NFκB pathway and repression of the antiapoptotic transcriptional factor Yin-Yang-1 (YY1) to allow Death Receptor 5 expression (Bonavida and Baritaki, 2011; Vivarelli *et al.*, 2022). In contrast, in human insulinomas, RKIP regulates cell cycle, but does not promote apoptosis (Zhang *et al.*, 2012a). This was additionally observed in an OV model, but metastasis was also tested and shown as suppressed in RKIP overexpressing cells (Li *et al.*, 2008), and shown in a genetically engineered mouse model of PRAD (Escara-Wilke *et al.*, 2015). RKIP suppresses intravasation by repressing Myc-mediated transcription of LIN28 downstream of its effects on the MAPK pathway (Dangi-Garimella *et al.*, 2009; Liu *et al.*, 2014a). LIN28 downregulation allows accumulation of the let-7 miRNA which inhibits the translation of High-mobility group

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AT-hook 2 (HMGA2) (Liu *et al.*, 2014a). HMGA2 promotes EMT through increasing transcriptional activity at TGFβ and Snail promoters, as well as expression of other tumor metastasis and signaling tools like MMP, IGFBP2, and syndecan-2 (Dangi-Garimella *et al.*, 2009; Ma *et al.*, 2009; Beshir *et al.*, 2010; Morishita *et al.*, 2013; Sun *et al.*, 2013a; Datar *et al.*, 2015a; Kou *et al.*, 2018). miR-185 has also been shown to inhibit HMGA2 translation via regulation by RKIP (Zou *et al.*, 2016). Just as Snail is regulated by RKIP, Snail is a transcriptional regulator of RKIP in metastatic PRAD cells. Additional transcriptional regulation of RKIP has been shown to be induced by binding of dihydrotestoterone with androgen receptor in prostate cells (Zhang *et al.*, 2012a) and via LncRNA GATA6 signaling (Gong *et al.*, 2020). RKIP also interacts with Melanoma Differentiation Associated gene-9 (MDA-9, Syntenin) to inhibit MDA-9 driven FAK/Src mediated migratory phenotypes (Das *et al.*, 2012).

RKIP expression influences both stromal and tumoral mediated mechanisms of metastatic outcomes (Bainer *et al.*, 2016). RKIP expression in TNBC reduces metastatic phenotypes of tumor-associated macrophages (TAM) (Datar *et al.*, 2015b; Frankenberger *et al.*, 2015). Patients can be stratified based on RKIP expression for immunotherapy by activating dendritic cells (DCs), i.e., patients with reduced RKIP after vaccination and activation of DC had impaired survival outcomes while those with higher RKIP levels prior to vaccination did not improve (Buschow *et al.*, 2017).

Treatment of PRAD cells with proteasome inhibitor NPI-0052 enhanced RKIP abundance, suggesting a degradation event that can downregulate RKIP (Baritaki *et al.*, 2009a, 2009b; Labbozzetta *et al.*, 2015). Indeed, CDK5 phosphorylation of RKIP marks it for degradation via autophagy in Parkinson's disease (Wen *et al.*, 2014). miR-224 directly represses RKIP translation in BRCA, facilitating bone metastasis (Huang *et al.*, 2012). STAD models have shown that the microRNAs miR-27a and miR-155 can inhibit translation of RKIP; the miRNA expression is driven by Bmi-1, an oncogene associated with multiple types of cancer metastasis (Kim *et al.*, 2004; Katoh and Katoh, 2009; Samson and Parvathi, 2023; Reyes-Carmona, 2025; Spoto *et al.*, 2026).

There are only a few instances in which RKIP has displayed prometastatic activity (Zhu *et al.*, 2005; Ma *et al.*, 2009). Merkel Cell Carcinoma intriguingly displays lowered pERK activation and high levels of RKIP, despite being a highly metastatic skin cancer subtype (Houben *et al.*, 2006), though pRKIP was not assessed in this study. The procarcinogenic and prometastatic activities are relatively understudied with regard to post-translational regulation and protein stability. There is evidence of degradation of RKIP via autophagy (Wen *et al.*, 2014), but in the context of metastasis, RKIP has been investigated thoroughly – providing potential opportunities for treatment.

Kruppel-like factors 4 and 5

KLF4 is a member of a large family of zinc-finger transcription factors. KLF4 both promotes and inhibits cancer progression through various mechanisms – its role as a Yamanaka factor implicates it as a stem cell marker, but some of its transcriptional targets are antitumorigenic/metastatic. KLF4 affects gene expression of a variety of gene targets associated with stemness, cancer progression, and metastasis through inhibiting or promoting expression in different contexts. KLF4 inhibits expression of *SPARC* (secreted protein acidic and rich in cysteine) (Zhou *et al.*, 2010) and CD44 (Yan *et al.*, 2016) while promoting expression of TIMP, E-cadherin, MMP2, β-catenin, and JNK1 expression (Yori *et al.*, 2010, 2011; Lai *et al.*, 2012; Zhang *et al.*, 2012b; Tiwari *et al.*, 2013; Li *et al.*, 2017a; Wu *et al.*, 2019).

KLF4 is downregulated in COAD and represses cyclin D1 expression by binding its promoter (Shie *et al.*, 2000). KLF4 is also downregulated in ESCA (Wang *et al.*, 2002), STAD (Wei *et al.*, 2005), ESCA metastases (Ma *et al.*, 2014b), but it is upregulated in skin squamous cell carcinoma (Chen *et al.*, 2008). KLF4 expression is increased in BRCA compared to adjacent-normal tissue (Foster *et al.*, 2000) and represses expression of the alpha subunit (LAMA3A) of Laminin-5, which is downregulated in BRCA (Miller *et al.*, 2001a, 2001b). In PAAD cells overexpression inhibits metastasis in orthotopic models (Wei *et al.*, 2008) and forced expression in PRAD cells inhibited migratory function (Wang *et al.*, 2010).

BRCA cells have KLF4-mediated stemness and migratory activity (Yu *et al.*, 2011). These observations were contradicted when KLF4 negatively regulated Snail expression and EMT in a HER2 model of murine BRCA (Yori *et al.*, 2010, 2011). KLF4 expression was shown to be associated with BRCA-brain (but not bone) metastases (Okuda *et al.*, 2013). Depletion of KLF4 promoted sensitivity of BRCA cells to the HER2 inhibitor lapatinib, and KLF4 was upregulated in response to lapatinib treatment in vitro (Farrugia *et al.*, 2015).

It was recently suggested that some of the discrepancy in KLF4 as a metastasis promoter or suppressor could arise from being present at different steps of the metastatic cascade. While KLF4 is predominantly associated as an inhibitor of EMT, upregulation of KLF4 after successful colonization at a secondary site could promote MET (Borrelli *et al.*, 2024).

Regulation of KLF4 is complex and occurs via many signaling pathways. KLF4 expression in COAD cells can be induced by APC and downregulated by induction of β-catenin signaling (Stone *et al.*, 2002), supplementary to the previously mentioned role of KLF4 in regulating β-catenin expression (Zhang *et al.*, 2012b). Further studies showed that this process is dependent on the transcription factor CDX2 to act on the KLF4 promoter (Dang *et al.*, 2001). Motility and invasion in some cancers appears to be dependent upon KLF4 expression, where miR-10b inhibited KLF4 translation, driving a more aggressive phenotype (Tian *et al.*, 2010; Su *et al.*, 2014; Xiao *et al.*, 2014). miR-103/107 appears to be a negative regulator in COAD metastasis (Chen *et al.*, 2012b). Further, miR-29a inhibits KLF expression in COAD and is associated with progression to metastasis in patients (Tang *et al.*, 2014a). In renal cell carcinoma, KLF4 promoters are hypermethylated suppressing expression in a tumor promoting fashion (Li *et al.*, 2013a).

KLF4 expression can be stimulated by hepatocyte growth factor (Lai *et al.*, 2012) and Notch1 via TWIST-mediated expression of Jagged (Chen *et al.*, 2014). STAT5A was recently shown to be a transcription factor that represses KLF4 expression in STAD cells; knockdown of STAT5A increased KLF4 expression and inhibited metastatic outgrowth following tail vein injection (Zang *et al.*, 2024).

The role of KLF4 in metastasis is not entirely tumor intrinsic. KLF4 drives stemness in HNSC cells via differentiation into endothelial-like cells to promote metastasis (Chen *et al.*, 2008). Perivascular cells also upregulate KLF4 prior to increasing deposition of ECM into the premetastatic niche, in a syngeneic melanoma model (Murgai *et al.*, 2017).

KLF5 was first identified as a potential tumor suppressor due to its deletion in PRAD and BRCA (Chen *et al.*, 2002; Rozenblum *et al.*, 2002). Like KLF4, there is evidence of KLF5 as both a metastatic promoter and suppressor, depending upon the cancer

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type and steps of metastasis assessed (reviewed in Lusby *et al.*, 2025). The complicated dichotomy of KLF5 depends upon the signaling input, cancer types, or other contexts that dictate its function. In APC^{min} $KRAS^{V12D/+}$ mice, haploinsufficiency inhibits tumor burden in the small intestine suggesting a pro-oncogenic role for KLF5 (Nandan *et al.*, 2010). Androgen signaling promotes KLF5 expression to drive CXCR4/CXCL12-mediated PRAD cell migration (Frigo *et al.*, 2009). KLF5 downregulation using siRNA inhibits androgen activated CXCR4 expression, demonstrating KLF5 as the mediator between androgen signaling and CXCR4 mediated migration. This was further validated in the context of COAD (Ma *et al.*, 2026). The mechanism of KLF5 regulation of CSCR4 expression was further elucidated showing that acetylation of KLF5 at K369 can be induced by TGFβ, and that acetylated KLF5 is essential for PRAD-bone metastasis, but not primary tumor growth (Zhang *et al.*, 2021a).

KLF5 knockdown increases anoikis in BRCA cells (Farrugia *et al.*, 2015), in part through acting as a transcription factor to increase *TNFAIP2* (TNF-induced protein 2) expression, which also promotes migration. This was also observed in nasopharyngeal carcinoma (Qian *et al.*, 2025b). THCA and LIHC cells treated with KLF5 siRNA display inhibited migration and invasion, with increased E-cadherin expression in vitro (An *et al.*, 2019; Ma *et al.*, 2014). The opposite was observed with overexpression of KLF5. Overexpression of KLF5 also rescues STAD migration and invasion after it was reduced with treatment of the antioxidant crocin (Zhou *et al.*, 2019). Recently, a small molecule inhibitor of KLF5 (ML264) decreased migration of COAD cells in a dose-dependent manner (Huang *et al.*, 2020). Collectively, KLF5 is observed as a metastasis promoter in these contexts.

In contrast, KLF5 knockdown in NSCLC cells decreased E-cadherin expression, a potential mechanism to inhibit EMT and reduce migration (Shimamura *et al.*, 2011). KLF5 overexpression inhibits KIRC in vitro and in vivo invasion, migration and metastasis, respectively (Fu *et al.*, 2017). A recent study in PRAD cells showed that KLF5 knockdown enhanced invasion, where IGF/STAT3 signaling was hyperactive in the absence of KLF5 (Ma *et al.*, 2026). Alternatively, KLF5 elicits differential effects on *Myc* transcription dependent on TGFβ treatment (Guo *et al.*, 2009; Guo *et al.*; 2009 Yeh *et al.* 2019): KLF5 knockdown is sufficient to inhibit *Myc* transcription in the absence of TGFβ, but KLF5 knockdown plus TGFβ promotes *Myc* transcription. This could contribute to the differentially observed roles as a metastasis promoter or suppressor.

While KLF4 competes with SP1 at promoter sites (Kong *et al.*, 2013, 2018), SP1 binds and enhances expression of KLF5 (Chen *et al.*, 2004). KLF5 has been documented as overexpressed in PAAD cells, and its expression is induced by IL-1β and HIF1α mediated mechanisms in the context of mutant KRAS (Mori *et al.*, 2009, 2021, 2024). Brca-associated protein-1 (BAP1) can deubiquitinate KLF5 to promote its stability and function in BRCA and SKCM (Qin *et al.*, 2015; Jia *et al.*, 2016, 2021; Fu *et al.*, 2017). The epigenetic regulator DNA methyltransferase 1 (DNMT1) can hypermethylate the KLF5 promoter, reducing its expression in KIRC cells (Fu *et al.*, 2017).

DLC1 (deleted in liver cancer 1)

DLC1 is a member of a larger family of molecules that share Rho GTPase activating protein (RhoGAP) domain, START domain and sterile alpha motif domain. DLC1 is frequently down-regulated in multiple cancers and confers tumor suppressing effects when re-expressed (Popescu and Goodison, 2014). RhoGAP molecules are critical regulators of GTP signaling by inactivating GTP-bound Rho proteins, RhoA, RhoB, RhoC, and CDC42. Resulting changes in actin cytoskeleton alters morphology, motility and invasion (Wong *et al.*, 2005; Holeiter *et al.*, 2008; Popescu and Goodison, 2014). However, there are also Rho-independent functions of DLC1 (Holeiter *et al.*, 2008; Barras and Widmann, 2013). SKCM models show a role for nuclear DLC1 as a metastasis promoter. Knockdown of DLC1 inhibited invasion and metastasis to lung in multiple SKCM cell lines (Yang *et al.*, 2020).

GAS1 (growth arrest specific 1)

GAS1 encodes an N-glycosylated, and glycosylphosphatidylinositol (GPI) anchored membrane protein that inhibits cell cycle progression (Del Sal *et al.*, 1994; Stebel *et al.*, 2000). Despite its primary role in regulating proliferation, GAS1 was reported to be metastasis suppressor of SKCM and STAD cells in experimental metastasis models (Gobeil *et al.*, 2008; Li *et al.*, 2016a). Knockout mouse models exhibit developmental defects that do not appear directly related to growth arrest (Lee *et al.*, 2001b; Liu *et al.*, 2002). Purported mechanisms for exerting these distinct phenotypes include: antagonism of Hedgehog signaling (Lee *et al.*, 2001a; Martinelli and Fan, 2007); signaling of AMPK/mTOR/P70S6K and EMT (Li *et al.*, 2016a), angiogenesis (Jimenez *et al.*, 2014) and apoptosis (Li *et al.*, 2016a). Importantly, discrimination between growth arrest) (Del Sal *et al.*, 1992), metastasis, and clinical stage of LUAD, BLCA, and COAD cancers (Jiang *et al.*, 2011; Wang *et al.*, 2012b; Sacilotto *et al.*, 2015) has not been extensively studied. Likewise, a soluble GAS1 isoform, tGAS1, has recently been discovered (Lopez-Ornelas *et al.*, 2014), but distinct roles in cancer have not been characterized. Treatment of PAAD cells with tGAS1 reduces pERK activation and invasion in vitro (Daniel-Garcia *et al.*, 2020). Likewise, TNBC cells displayed reduced angiogenesis with tGAS1 over-expression in orthotopic tumors (Jimenez *et al.*, 2014).

LIFR (leukemia inhibitory factor receptor)

Chen and colleagues first reported that LIFR functions as a metastasis suppressor in BRCA models (Chen *et al.*, 2012). Similar findings have been reported in different BRCA models (Iorns *et al.*, 2012). LIFR expression is downstream of miR-9 and upstream of Hippo/YAP signaling (Luo *et al.*, 2015). However, in LIHC models, suppression appears to occur via inhibition of PI3K/AKT signaling (Luo *et al.*, 2015). In GBM models, invasion appears to be related to macrophage-derived oncostatin M signaling through LIFR and activation of STAT3 (Hara *et al.*, 2021). Those signals are presumed to regulate the EMT-MET state of the cells. LIFR-mediated AKT activation is regulated by ERK phosphorylation of LIFR at serine 1044 (Shao *et al.*, 2019), which in PRAD, promotes migration, invasion, and proliferation.

Regulation of invasion

Just as surface adhesion molecules are critical for metastasis, invasion is an essential step for neoplastic cells to dissociate from the primary tumor, enter a transit compartment, and migrate between different tumor microenvironments. Invasion is typically mediated by proteases that renovate the ECM. Proteolytic activity is regulated at multiple levels, leading to differentially observed impacts on metastasis and survival, depending upon the milieu in which they are operating.

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Matrix metalloproteinases (MMP) and tissue inhibitors of MMP (TIMP)

In this section, we will use a large class of proteases – the MMP – and protease inhibitors – the TIMP – to illustrate the context-dependency of metastasis genes (gene products). Other classes of proteases are also commonly involved in metastasis and readers are referred to several excellent reviews for more information (Bernacki *et al.*, 1985; Nakajima *et al.*, 1988; Duffy, 1992; DeClerck *et al.*, 1997; Price *et al.*, 1997; Stephens *et al.*, 1998; Koblinski *et al.*, 2000; Rochefort *et al.*, 2000; Sanderson, 2001; Decock *et al.*, 2005; Arvatz *et al.*, 2011; Mason and Joyce, 2011; Pawar *et al.*, 2019).

MMP make up a family of secreted (17 total) or membrane bound (6 total) proteases that degrade ECM substrates. There are specific and overlapping substrates throughout the family (Turunen *et al.*, 2017). MMP were first distinguished by their primary substrate, acting as collagenases, gelatinases, stromelysins, and matrilysins. However, most MMP are now recognized to cleave multiple overlapping substrates (Laronha and Caldeira, 2020; Li *et al.*, 2023). MMP are synthesized in a pro-from, where their protease catalytic sites require a cleavage of the MMP near the N-terminus to free the C-terminal side to interact with and cleave target substrates (Piperigkou *et al.*, 2025). Alteration of MMP activity or expression are associated with several pathologies (Laronha and Caldeira, 2020). Genetically engineered knockout mice have been generated for each MMP, and they exhibit a variety of phenotypes ranging from altered presentation of obesity, tumor formation, cardiomyopathies, infection, and other documented phenotypes (Iyer *et al.*, 2012).

The presumptive activity of MMP in metastasis has always been invasion, which is generally correct. However, some MMP have nonproteolytic functions (Shay *et al.*, 2015; Piperigkou *et al.*, 2025) and many MMP are involved in multiple other steps of the metastatic cascade (McDonnell and Fingleton, 1993; Chambers and Matrisian, 1997; Fingleton *et al.*, 1999; McDonnell *et al.*, 1999; Deryugina and Quigley, 2006; Lynch, 2011; Tauro and Lynch, 2018; Winer *et al.*, 2018; Gonzalez-Avila *et al.*, 2019; Piperigkou *et al.*, 2025).

By archiving known substrates of MMP and TIMP that regulate MMP function, Gonzalez-Avila *et al.* (2019) and Piperigkou *et al.* (2025) categorized their roles in cancers. Both proteolytic and nonproteolytic functions of MMP promote angiogenesis, migration/invasion, intravasation, extravasation, and premetastatic niche formation (Winkler *et al.*, 2004; Shay *et al.*, 2015; Quintero-Fabian *et al.*, 2019; Piperigkou *et al.*, 2025). MMP can also alter adhesion in the contexts of extravasation or colonization (Shoari *et al.*, 2024, 2025; Biswas *et al.*, 2025).

Despite evidence of MMP being drivers of invasion and metastasis, early clinical trials of MMP inhibitors (MMPi) failed to improve patient outcomes (Coussens *et al.*, 2002; Shay *et al.*, 2015; Winer *et al.*, 2018). There were several explanations for the negative results, including lack of inhibitor specificity, deleterious side effects, and possibly pharmacokinetics and pharmacodynamics (Winer *et al.*, 2018). Additionally, MMP enzymatic activity was not consistently measured, making revisitation of MMPi strategy worth revisiting (Fingleton, 2008; Tauro and Lynch, 2018; Winer *et al.*, 2018).

As expected, survival generally correlates inversely with mRNA (TCGA) or protein (CPTAC) expression (Table 7). In OVCA, MMP14 serves as a driver of metastasis, but does not appear to be an independent predictor of prognosis (Vos *et al.*, 2021). MMP2 and MMP9 are mostly described as prometastatic. MMP2/9 are implicated in metastasis through several mechanisms (Duffy *et al.*, 2000, 2008; Zucker and Vacirca, 2004; Jezierska and Motyl, 2009; Shoari *et al.*, 2024, 2025). In BRCA metastasis to the bone, Tauro and Lynch (2018) review and describe the roles of MMP1, 2, 3, 7, 9, 13, and 14 as metastasis promoters. They further describe how MMP2 is a critical component of each step of the metastatic cascade, through proteolytic cleavage of both matrix substrates, as well as by cleaving pro-forms of protumorigenic cytokines. Similarly, PRAD cells metastasizing to bone utilize MMP3 to promote vascularization at the metastatic site by altering cell signaling in endothelial tube cells (Frieling *et al.*, 2020). Likewise, BLCA MMP2/9 are rate-limiting enzymes of collagen IV destruction to invade the basement membrane prior to intravasation (Black and Dinney, 2007; Watroba *et al.*, 2021).

MMP can promote signaling pathways by activating prometastatic cytokines or growth factors. They can also cleave ECM to free signaling molecules, degrade of inhibitors, or cleave of prosignaling peptides into their active forms (Kessenbrock *et al.*, 2010). For example, MMP2, 9, and 14 activate TGFβ through cleavage of latent TGFβ binding protein in the ECM. MMP7 can cleave and release RANKL to drive NFκB signaling in bone metastasis (Lynch *et al.*, 2007). MMP7 also cleaves cell-membrane attached heparin-bound growth factor into its soluble form driving internalization and cytosolic signaling of ErbB4 (Lynch *et al.*, 2007). MMP3 and 7 can cleave E-cadherin into a soluble form that acts in a paracrine fashion to promote cellular invasion (Noe *et al.*, 2001). In contrast, in oral squamous cell carcinoma, MMP9 can inhibit angiogenic properties through increasing levels of endostatin and angiostatin, impeding endothelial cell proliferation (Vilen *et al.*, 2013). MMP8 can also enhance tumor-ECM adhesion correlating with reduced lung metastases from a syngeneic MMP8 overexpressing SKCM line (Gutierrez-Fernandez *et al.*, 2008).

MMP expression is not restricted to tumor cells. MMP9 is secreted by neutrophils to promote prometastatic angiogenesis prior to intravasation from the primary site (Poto *et al.*, 2022). Circulating monocytic myeloid derived suppressor cells (mono-MDSCs) secrete MMP9 to promote metastasis to lung (Zhang *et al.*, 2020d, 2020c). $VEGFR1^{+}$ hematopoietic progenitor cells and bone marrow-derived endothelial cells express MMP9 prior to cancer cell arrival at the site (Kaplan *et al.*, 2005, 2006). Stromal MMP9 is an important contributor to COAD metastasis to the liver, where MMP9 null mice displayed reduced metastasis formation by splenic injection of COAD cells (Gorden *et al.*, 2007). Similarly, $MMP13^{-/-}$ mice display reduced liver steatosis induced by a high-fat diet leading to a subsequent reduction in COAD-to-liver metastases and reduced extravasation (Mendonsa *et al.*, 2015b). MMP2 secretion from fibroblasts also drives TGFβ mediated matrix remodeling, promoting BRCA growth in vitro (Bates *et al.*, 2015). Kessenbrock *et al.* (2010) review other stromal constituents that express proteases (MMP and ADAMs) or their inhibitors (TIMPs).

Expression of MMP across cancers and stroma is regulated by a variety of mechanisms and signaling cascades. Mediation via cytokine signaling, especially in the context of angiogenesis (reviewed in Quintero-Fabian *et al.*, 2019). Growth factors EGF, HGF, and FGF3/4 drive expression of either MMP2 or MMP9 in some cancers (Kondapaka *et al.*, 1997; Hajitou *et al.*, 1998; Li *et al.*, 1998). MMP9, specifically, is well documented to be upregulated through several mechanisms ranging from signaling pathways (NFκB, AKT, β-catenin), hypoxia, interleukins, and microRNA (Andela *et al.*, 2003; Barillari, 2020). CD44 stimulation with monoclonal antibodies, but not canonical ligands, can induce MMP2 expression in SKCM (Takahashi *et al.*, 1999). Meanwhile, IFNγ reduces MMP2

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Table 7. Human protein atlas potential prognosis description (TCGA Kaplan–Meier plotting from expression) and protein (tumor vs normal) abundance (CPTAC) of MMP in cancer

MMP	Membrane bound or secreted	Prognosis	Cancers	Higher or lower protein abundance (CPTAC) in cancer compared to normal
MMP1	Secreted	Unfavorable	CEHC, LIHC, KIRC	Only significantly more abundant, nonsignificant difference in other cancers.
MMP2	Secreted	Not prognostic	N/A	Higher, lower, or nonsignificantly changed abundance across several cancer types compared to normal tissue.
MMP3	Secreted	Unfavorable	CEHC, LUAD, PAAD	No significant difference in abundance compared in normal tissue compared to cancer.
MMP7	Secreted	Unfavorable	LIHC	Significantly higher abundance in colon adenocarcinoma, pancreatic ductal adenocarcinoma.
MMP8	Secreted	Not prognostic	N/A	Significantly lower abundance in lung, hepatocellular carcinoma; not significantly altered in others.
MMP9	Secreted	Unfavorable	LIHC, KIRC	Lower abundance in lung, hepatocellular carcinomas, higher abundance in head and neck squamous carcinoma.
MMP10	Secreted	Unfavorable	LIHC	No significant difference in abundance compared in normal tissue compared to cancer.
MMP11	Secreted	Unfavorable	GBM, LUAD, OV	No significant difference in abundance compared in normal tissue compared to cancer.
MMP12	Secreted	Unfavorable	LIHC, LUAD, KIRC	Significant increase in abundance in Lung squamous cell carcinoma, head and neck squamous carcinoma, and pancreatic ductal adenocarcinoma.
MMP13	Secreted	Unfavorable	PAAD	No significant difference in abundance compared in normal tissue compared to cancer.
MMP14	Membrane bound	Unfavorable	LUAD, OV	Significantly upregulated in lung (adenocarcinoma, squamous cell carcinoma) cancer, colon adenocarcinoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, pancreatic ductal adenocarcinoma, renal cancer.
MMP15	Membrane bound	Favorable and unfavorable	Favorable: KIRC Unfavorable: CEHC	Significantly higher abundance in endometrial cancer, lung squamous cell cancer compared to normal tissue. Significantly lower abundance in Hepatocellular carcinoma compared to normal tissue.
MMP16	Membrane bound	Favorable	GBM	No significant difference in abundance compared in normal tissue compared to cancer.
MMP17	Membrane bound	Unfavorable	OV	No significant difference in abundance compared in normal tissue compared to cancer.
MMP19	Secreted	Unfavorable	KIRC	Only significantly more abundant in pancreatic ductal adenocarcinoma versus normal tissue.
MMP20	Secreted	N/A	N/A	N/A
MMP21	Secreted	N/A	N/A	N/A
MMP23	Secreted	Unfavorable	KIRC	Significantly less abundant in lung adenocarcinoma, lung squamous cell carcinoma, and hepatocellular carcinoma.
MMP24	Membrane bound	Favorable	KIRC	N/A
MMP25	Membrane bound	Favorable	HNSCC	No significant difference in abundance compared in normal tissue compared to cancer.
MMP26	Secreted	N/A	N/A	Significantly lower abundance in uterine cancer than normal tissue
MMP27	Secreted	N/A	N/A	N/A
MMP28	Secreted	Unfavorable	PAAD	Lower significant abundance in lung cancer (adenocarcinoma; squamous cell carcinoma)

production in RCC cells (Gohji *et al.*, 1998), and astroglioma cells (Qin *et al.*, 1998). MMP 2, 9, and 14 are inhibited by RECK: this is regulated by the requirement of RECK glycosylation at N297 (MMP9 inhibited secretion) or N352 (MMP2 inhibited activity) (Sasahara *et al.*, 2002; Noda *et al.*, 2003; Clark *et al.*, 2007; Noda and Takahashi, 2007). RECK-mediated inhibition of MMP can occur through direct interactions, but RECK expression also negatively correlates with expression of some MMP (Takahashi *et al.*, 1998).

As enzymes, mere expression is insufficient to address MMP activity. As with other proteases, MMP enzymatic activity is intricately regulated by selective tissue inhibitors of metalloproteinases (TIMP). TIMP constitute a family of four MMP inhibitors. They also interact with integrins, A-Disintegrin And Metalloproteinases (ADAM), and various cytokine/growth factor receptors (Arpino *et al.*, 2015; Eckfeld *et al.*, 2019). Importantly, the ratio between MMP and TIMP expression regulates MMP activity which, in turn,

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determines cancer aggressiveness, staging, and metastasis (Bramhall *et al.*, 1997; Kugler, 1999; Andela *et al.*, 2003).

Despite the inhibitory role of TIMP, TIMP1 expression can be associated with poor prognosis The differences between TIMP family members, their interactors, and roles in signal transduction in cancer are summarized in Jackson *et al.* (2017) and cancer-type specific contexts associated with poor prognosis are reviewed in Eckfeld *et al.* (2019).

In addition to cancer-type specific roles of TIMPs, studies on TIMPs in various physiological contexts exhibit mixed effects across tissues. TIMP1 knockout mice display increased fibrosis in response to injury in the liver, but not fibrosis in lung (Arpino *et al.*, 2015). Inflammatory signaling is, however, elevated in both liver and lung. TIMP2$^{-/-}$ mice exhibit cardiac collagen disorganization, where TIMP2 regulates MMP14 activity (Kandalam *et al.*, 2010). TIMP3$^{-/-}$ mice also display increased degradation of collagen and fibronectin in lung tissues (Leco *et al.*, 2001; Martin *et al.*, 2003). TIMP3$^{-/-}$ further leads to kidney and heart fibrosis following injury (Kassiri *et al.*, 2009a, 2009b).

Some key principles emerging from analysis of MMP and TIMP in metastasis are: (1) expression levels are not always correlated with activity; (2) proteolytic cleavage is dependent upon stoichiometry of the proteases and their inhibitors; (3) the impact of the proteases and their inhibitors can be direct or indirect; (4) stroma-derived molecules contribute to the promotion or inhibition of proteolysis; (5) different members of each family play tissue-specific roles and, (6) each of the MMP and TIMP have functions that are not necessarily associated with their proteolytic activity. Those principles apply to other protease families as well.

SERPINB5/Maspin

Maspin is a serine protease inhibitor encoded by *SerpinB5* (Berardi *et al.*, 2013). So, its first presumed mechanism of action is related to regulation of invasion. Maspin directly binds pro-uPA via its reactive site loop, thereby blocking plasmin-mediated activation and promoting uPA/uPAR internalization which, in turn, limits ECM remodeling (Yin *et al.*, 2006). However, Maspin function is significantly more complex (Bailey *et al.*, 2006). Maspin also suppresses tumor cell detachment by stabilizing adhesion complexes. Maspin blocks VEGF- and bFGF-driven angiogenesis and reduces tumor microvessel density. Maspin's antiangiogenic activity is distinct from its inhibition of tumor cell migration (Zhang *et al.*, 1997, 1999, 2000). SERPINB5 is a cytoskeleton-binding protein that regulates epithelial cell architecture. Loss disrupts actin organization and induces EMT-like changes (altered E-cadherin localization and upregulation of EMT transcription factors) and accelerates microtubule growth. Loss or dysregulation of SERPINB5 may facilitate epithelial plasticity and invasion (da Silva *et al.*, 2025).

Nuclear localization of Maspin is essential for its regulation of tumor growth and metastasis (Goulet *et al.*, 2011). Maspin was initially discovered as a tumor and metastasis suppressor following transfection into MDA-MB-435 cells in nude mice (Zou *et al.*, 1994). Suppression of invasion and/or metastasis has been described in PRAD (Abraham *et al.*, 2003; Bernardo *et al.*, 2011) by reprogramming a subset of HDAC1-regulated genes, down-regulating EMT and TGFβ signaling. Maspin suppressed MMP9, uPA, and uPAR, and enforced β1-integrin–dependent polarized adhesion in collagen I–rich environments.

However, in a study of 132 tumor samples from patients with NSCLC, SERPIN5 overexpression in the cytoplasm resulted in poor prognosis (Hirai *et al.*, 2005). Also, SERPINB5 is significantly overexpressed and demethylated in LUAD correlating with reduced overall and progression-free survival. SERPINB5 was likewise correlated with the development of muscle invasive BLCA (Sugimoto *et al.*, 2004), CESC (Hao *et al.*, 2025), and PAAD (Lim *et al.*, 2004; Cao *et al.*, 2007). Using LUAD cell lines (A549 and PC9), SERPINB5 knockdown suppressed migration, invasion, and epithelial–mesenchymal transition (EMT), while SERPINB5 overexpression enhanced these metastatic phenotypes. Gene set enrichment analyses linked high SERPINB5 expression to EMT, TNFα–NFκB, IL-17, HIF-1, MYC, E2F, and mTORC1 signaling pathways, suggesting that SERPINB5 promotes metastasis by driving EMT and activating oncogenic and inflammatory signaling programs (Tian *et al.*, 2020). Likewise, PAAD metastasis, invadopodia formation and MMP activity were enhanced when overexpressed (He *et al.*, 2023b). Over-expression in COAD cell lines promoted EMT, MMP2 and MMP9, VEGF (Liu *et al.*, 2024a).

Stefin A/cystatin A

Another protease inhibitor, Stefin A, belongs to the cysteine protease inhibitor family. Transfection of Stefin A into human ESCA cells reduced cathepsin B and inhibited Matrigel invasion. Overexpression of Stefin A decreased lung metastasis in a mouse xenograft model (Li *et al.*, 2005). Likewise, re-expression of Stefin A in murine mammary cancer decreased bone metastasis in vivo (Parker *et al.*, 2008). Thus, the presumptive mechanism of action is through reduced cathepsin B activity (Withana *et al.*, 2012). Supporting this mechanism, shRNA knockdown of cathepsin B decreased lung metastasis in syngeneic mice without affecting the orthotopic mammary tumor growth. In LUAD cells, overexpression of Stefin A suppressed EMT and promoted MET, suggesting an alternative mechanism of action (Ma *et al.*, 2018b). Demethylation of DNA increased Stefin A expression in those same cells, suggested DNA methylation as a potential cause of decreased expression in cancer (Wang *et al.*, 2021b).

In tissue sections, Stefin A expression is heterogeneous in metastases. It is expressed where there is interaction with stromal cells, but not in the center of metastases. The expression pattern could be due to differential oxygenation, response to external signals from stromal cells, or the loss of ability to produce the molecule (Li *et al.*, 2005).

Summary and implications

While the list of molecules reviewed here is long, it is still incomplete. We have opted to use several key molecules for which there are relatively abundant data in an attempt to illustrate several key points. Foremost, metastasis is a highly complex, multigenic phenotype. A one gene–one phenotype explanation of metastasis has long been discounted and analysis of the genes and gene products discussed here exemplify that point. Coordinated spatial and temporal gene expression is absolutely essential for cancer dissemination to form secondary foci. Molecules that may be necessary for metastasis are not necessarily sufficient. That metastasis suppressors – defined by their ability to inhibit metastasis without blocking primary tumor development – exist demonstrates that tumorigenicity and metastasis are distinct genetic diseases. The fact that most of the genes and gene products described here have diametrically opposite results in different tumor types highlights that metastasis is indeed a complex, polygenic disease, impinged by combinations of differential transcription, translation, presence or absence of isoforms, post-translational modifications, interactors (at both

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the cellular and molecular levels), regulators (signaling and epigenetic), protein stability, and protein location.

Single cell analysis, while contributing insights, is also limited because it results in probabilistic predictions since it is currently impossible to know whether a given cell is actually THE 1/<0.00001% of cells that eventually successfully succeed in metastatic colonization. Transcriptomic studies do not necessarily take into account whether a protein encoded by an mRNA is proportionately present. This issue is further complicated by enzymes whose activity is not necessarily proportionate to the number of molecules present and which are regulated by other co-expressed molecules and the stoichiometric relationships of those pairs. Thus, there is a strong danger in extrapolating findings using a single technique.

Complex genetic diseases are contributed to by sometimes 10s to 100s of genes simultaneously. The genetic backgrounds upon which those genes are expressed have profound effects on the efficiency of metastasis. All of the molecules described here function in pathways or complexes with agonistic or antagonistic partners. Discussion of pathways is often oversimplified as linear rather than arbors of branches. Signaling is, in fact, a web of interconnecting pathways. Thus, there are redundancies in the system. By analogy, there are many roads leading to Rome. When blocking one road, cells find ways to circumvent that blockade. Redundancy is one mechanism that results in resistance to antimetastatic therapies or circumvention of metastasis suppressors.

Another limitation of this review is that we have mostly focused on molecules that have *functional* data associated with them and metastasis. We also acknowledge that many of the data reported here and in cited papers do not always discriminate cancer subtypes. Therefore, readers are cautioned not to extrapolate findings reported here to all subtypes since there are clearly differential effects of metastasis genes that are subtype- or cancer-specific.

To illustrate this point, we compared publicly available datasets examining gene expression data for four metastasis-associated molecules (readers can perform the same analysis with other genes and cancer types) (Figure 2). GSN, BRMS1, NME1, and TIMP4 expressions are examined with their relationship to development of bone or lung metastases. What is clearly illustrated is how

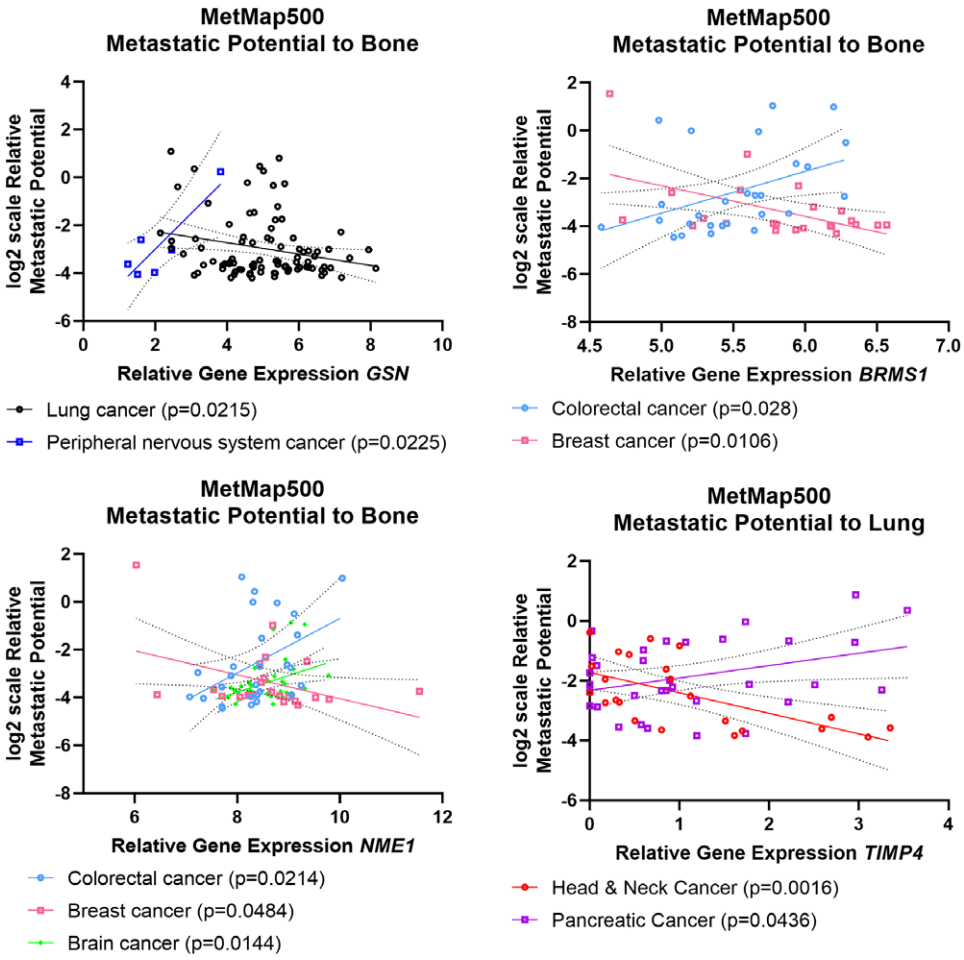


Figure 2. Representative data showing that metastasis regulatory gene expression exhibits conflicting patterns of metastatic efficiency in different cancer types. Data were derived from MetMap500 Relative Metastatic Potential (Jin *et al.* 2020) and Gene Expression (Cancer Cell Line Encyclopedia, CCLE (Ghandi *et al.*, 2019) was accessed via DepMapPortal (Tsherniak *et al.*, 2017). Representative data are shown to demonstrate that gene expression correlation (linear regression) with metastasis (Metastatic Potential as defined in Jin *et al.* (2020) can differ based on context. Shown are examples significantly ($p < 0.05$) positively or negatively correlated CCLE gene expression of four metastasis suppressors (GSN, BRMS1, NME1, TIMP4) with MetMap500 metastatic potential to bone (*a*–*c*) or lung (*d*) cancer types. Dotted lines = 95% confidence interval. (*a*) Correlation of cell line GSN expression with metastatic potential to bone in lung cancer cell lines (black, negative correlation) and peripheral nervous system cancer cell lines (blue, positive correlation). (*b*) BRMS1 expression correlated to metastatic potential to bone in colorectal cancer (blue, positive correlation) and breast cancer (pink, negative correlation) cell lines. (*c*) NME1 expression correlated to metastatic potential to bone in colorectal cancer (blue, positive correlation), breast cancer (pink, negative correlation) and brain cancer (green, positive correlation) cell lines. (*d*) TIMP4 expression versus lung metastatic potential in head and neck cancer (red, negative correlation) and pancreatic cancer (purple, positive correlation) cell lines.

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correlations of expression and probability of metastasis are positive or negative for each metastasis suppressor, depending upon tumor type. We did not find a single example where a gene is always positively or negatively correlated with metastasis development.

What is the take-home message? Our title says it all – metastasis genetic and epigenetic function are context dependent. All molecules regulating metastasis are regulated at multiple levels (epigenetics, transcription, splicing, translation, stability). And most molecules have multiple functions, likely determined by the molecules with which they are associated. The multi-dimensional relationships represent a problem that machine or language learning algorithms can hopefully help solve. Although disheartening in some respects, it is clear that no single gene will explain nor solve the problem of metastasis.

As a result, using these genes as biomarkers to predict probability for developing metastasis has been frustrating and has fallen short of optimistic predictions. We predict that *combinations* of these molecules will eventually emerge as helpful predictive biomarkers, just like combinations of surface molecules are now used to define immune cells or cancer subtypes. Predictions will also be facilitated by more precise defining of cellular contexts. As single cell analyses of various tumor microenvironments become more well defined, the contexts defining cellular responses will be better defined. Heterogeneity of both the cancer cells and the myriad TME experienced during transport of metastatic cells await more definitive understanding before direct applications will be possible. Importantly, many of the interactions are transient and the cells' responses are temporary. One must keep in mind that most current technologies allow only 'snapshots' rather than 'video' of events leading to development of metastasis.

There remains hope that some of the metastasis-associated genes and gene products can become targets for selective treatment (i.e., inhibiting metastasis promoting molecules, protease inhibitors, etc.) or treatments themselves (i.e., metastasis suppressors). Again, that promise will be delayed until the field develops a better handle on regulation and cofactors involved.

Despite the complexity highlighted in this review, increases in the knowledge related to metastasis regulation has already led to improvements in survival and quality of life for patients with many types of cancer. Whereas, 5-year survival with stage-IV cancer was almost unheard of a few decades ago, some patients have survived for decades. As metastasis genetics and epigenetics become increasingly well defined, we expect that outcomes will further improve.

Supplemental material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033583526100201.

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