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Immunological responses can have both pro- and antitumour effects: implications for immunotherapy

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Immune responses influence the development and progression of a malignancy. The tumour can also manipulate the immune system to its own ends, often resulting in an ineffective or transient antitumour response. An appreciation of the complexity of these host–tumour interactions is therefore important for the development of more-effective cancer therapies. This article highlights some prominent mechanisms whereby tumours escape recognition and destruction by the host immune system, thus facilitating disease progression. One important consequence of tumour escape is that an antitumour immune response may unintentionally lead to the outgrowth of less immunogenic or more apoptosis-resistant tumour escape variants, which possess enhanced tumourigenic potential. Insights into the molecular mechanisms of cancer evasion and the complexity of the ever-changing interactions between host and tumour will enable a more rational design of antitumour therapies and may help not only explain disease recurrence, but also identify potential targets for therapeutic interventions. This article also offers a brief review of preclinical animal models, which are essential tools in the study of tumour immunology and cancer biology, particularly those that recapitulate the chronic nature of host–tumour interactions and help guide the development and testing of new therapies.

Despite years of debate, it is now generally accepted that the immune system is capable of recognising and destroying cancer cells in a process termed immunosurveillance (Refs 1, 2). Evidence supporting this includes (1) the ability to detect and stimulate specific immune responses from tumour-bearing animals (Ref. 3) and patients with cancer (Refs 4, 5), including tumour-specific antibodies and T cells, and (2) the higher incidence of cancer development in immunocompromised individuals (Refs 6, 7). The immune system can distinguish

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transformed cells by recognising tumour-associated antigens (TAAs), including the over- or under-expression of normal proteins or mutated self-products (Ref. 8). Despite this, the immune system does not always detect and kill all cancerous cells; such cells have evolved strategies to escape host immunosurveillance, including tumour-induced mechanisms of tolerance, immunosuppression or diminished immune recognition. Therefore, to appreciate the role the immune system plays in shaping tumour growth and its possible exploitation as an antitumour modality, it is important to understand how cancer cells circumvent immune attack.

There are several major questions that require further elucidation. How do tumour cells interact with the host, and how do these interactions change with progressive tumour growth? What mechanisms exist that permit tumours to progress despite the presence of tumour-specific immune responses? Why do some therapies work in one patient but not in others? How can a greater understanding of host–tumour interactions be applied towards the design of treatment strategies? What are the best experimental models to investigate these mechanisms and to test new therapies? These questions cover a broad and complex topic that has been considered for a number of years and will certainly be the subject of future intensive investigations.

A particular focus of tumour immunologists is the translational possibilities of harnessing the host immune system for use in prophylactic and therapeutic strategies that combat cancer development and progression. These therapies might include manipulations of the host to overcome tumour-induced suppression and tumour escape by immune selection pressures. Because the immune system has now been shown to affect tumour growth positively and negatively, and since the presence of cancer has been shown to downmodulate immune reactivity, it is important that aspects of both cancer biology and immunology be integrated to achieve a better understanding of the dynamics and complexity of host–tumour interactions.

Tumour development and metastases formation

It has long been recognised that most tumours become more clinically and biologically aggressive over time (Refs 9, 10). Neoplastic cells are of greatest clinical significance when malignant behaviour progresses to stages of invasion and metastasis. Metastases are responsible for the majority of cancer deaths, due in part to damage to other organ systems and the inability of conventional therapies, such as radiation and chemotherapy, to eradicate resistant or disseminated disease effectively.

There are two major theories on metastases development. First, it is generally well accepted that tumour progression to metastasis proceeds through a succession of genetic and epigenetic events in a multistep process that results in the expansion of tumour cell clones with a selective survival or growth advantage. Some of these early mutations might also affect genomic stability, thus facilitating the accumulation of additional mutations and the outgrowth of more-aggressive subclones (Ref. 11). Therefore, tumour progression occurs by overcoming growth restrictions through the accumulation of genetic and epigenetic alterations (Ref. 12). Colonisation of metastases then relies on the relationship between the tumour cell and the host tissue environment, which may determine the organ-specific pattern of metastases (Ref. 13). This model of metastases development has recently been challenged, due primarily to the identification of similar gene expression profiles between primary tumours and the metastases derived from them (Ref. 14). The second model suggests that somatic alterations already exist within the dominant cancer cell population of the primary tumour and the ability to metastasise is determined early during tumourigenesis (Ref. 15). It has also been shown that the genetic background (polymorphisms) of the host might influence the metastatic capacity of tumour cells (Ref. 16).

For metastases to form, malignant cells must first have the ability to migrate through adjacent tissue, lymphatics and blood vessels. These circulating cells have been shown to be particularly susceptible to killing by natural killer (NK) cells or monocytes (Ref. 17). If these potentially metastatic cells manage to avoid or survive this innate immune attack, they must then establish themselves at secondary or distal sites. The successful establishment of a metastasis would then depend on the local microenvironment for structural support (extracellular matrix) and growth factors.

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It has been proposed that immune cells responding to the 'danger signals' of a tumour cell (Ref. 18) or to TAAs may be a source of these growth factors and thus aid in metastases formation. Therefore, the host immune system can play the dual role of tumour cell elimination and tumour cell growth promotion. Which role predominates will depend on the local microenvironment and possibly the aggressiveness of the tumour and its ability to skew or subvert responding immune cells to serve the needs of the developing tumour. Another factor is the generation of drug-resistant malignancies as a result of therapy, whereby treatment selects for more-aggressive tumour cells that have the necessary attributes to resist the therapy. Similarly, tumour progression may result from the escape of recognition or attack by host defence mechanisms. This is a dynamic relationship in which aberrant cells arise and are eliminated by components of either the innate or adaptive immune responses. The relationship between host and tumour is therefore bidirectional in nature, with the host immune system mounting a pro-inflammatory response to eradicate the tumour, and the tumour employing mechanisms either to overcome or to usurp this inflammatory response. Consequently, although the goal of the immune response is to eliminate the tumour, the response itself can also have tumour-promoting consequences.

Bidirectional consequences of inflammatory responses

The link between inflammation and cancer was first described by Virchow in 1863 (Ref. 19). Many cancer types are associated with a chronic or persistent inflammation: some examples include colon cancer with inflammatory bowel disease, lung cancer with asbestosis, and liver cancer with hepatitis viral infections (Ref. 20). During the struggle between a developing tumour and the immunosurveillance mechanisms of the host, both the innate and adaptive arms of the immune system are activated and an inflammatory response ensues. This response might facilitate the elimination of abnormal cells, particularly in its acute phase. However, once the inflammatory response becomes chronic, it might also be modulated by tumour cells to enhance their own growth, either directly or indirectly, through immunosuppression of the host. In an inflammatory environment, transformed or genetically unstable cells have the opportunity to accumulate further genetic alterations, which can make them more resistant to immune attack. Whether a tumour develops or is eliminated depends, in part, on the balance between the effector and regulatory functions of the immune system and is likely to shift depending on the in situ signals and the capacity of the host to modulate those signals (Fig. 1). As will be discussed later, the predominance of immune regulatory cells can impose an immunosuppressive effect on potential antitumour cells, thus tipping the balance in favour of tumour growth by immune evasion.

Further studies have revealed that tumour progression can be potentiated by pro-inflammatory responses within the tumour microenvironment and by downregulation of the immune response by tumour-derived factors (Ref. 20). Indeed, a tumour has been described as 'a wound that does not heal' (Ref. 21). Many para-neoplastic syndromes in patients with cancer are also mediated by immune responses, usually antibodies against tumour proteins that crossreact with normal host cells (Refs 22, 23). Therefore, inflammation may render the host susceptible to the development of new tumours directly, through the effects of inflammatory compounds on host tissues, or indirectly, through immunosuppression; together, these processes lead to the facilitation of tumour growth and metastatic formation.

Many tumour lesions contain immune cells such as dendritic cells (DCs), macrophages and T cells termed tumour-infiltrating lymphocytes (TILs). TILs contain a high level of TAA-specific T cells, which despite their activated phenotype are functionally compromised. It has become evident that these TILs can produce cytokines or other growth factors that assist tumour growth (Ref. 24), and that tumours can actively recruit these cells through the production of chemotactic factors (Ref. 25).

Some inflammatory mediators, including prostaglandins (e.g. PGE_2), inflammatory cytokines, reactive oxygen species (ROS) and nitrogen intermediates, confer a survival advantage to tumour cells by inducing resistance to apoptosis, pro-tumourigenic

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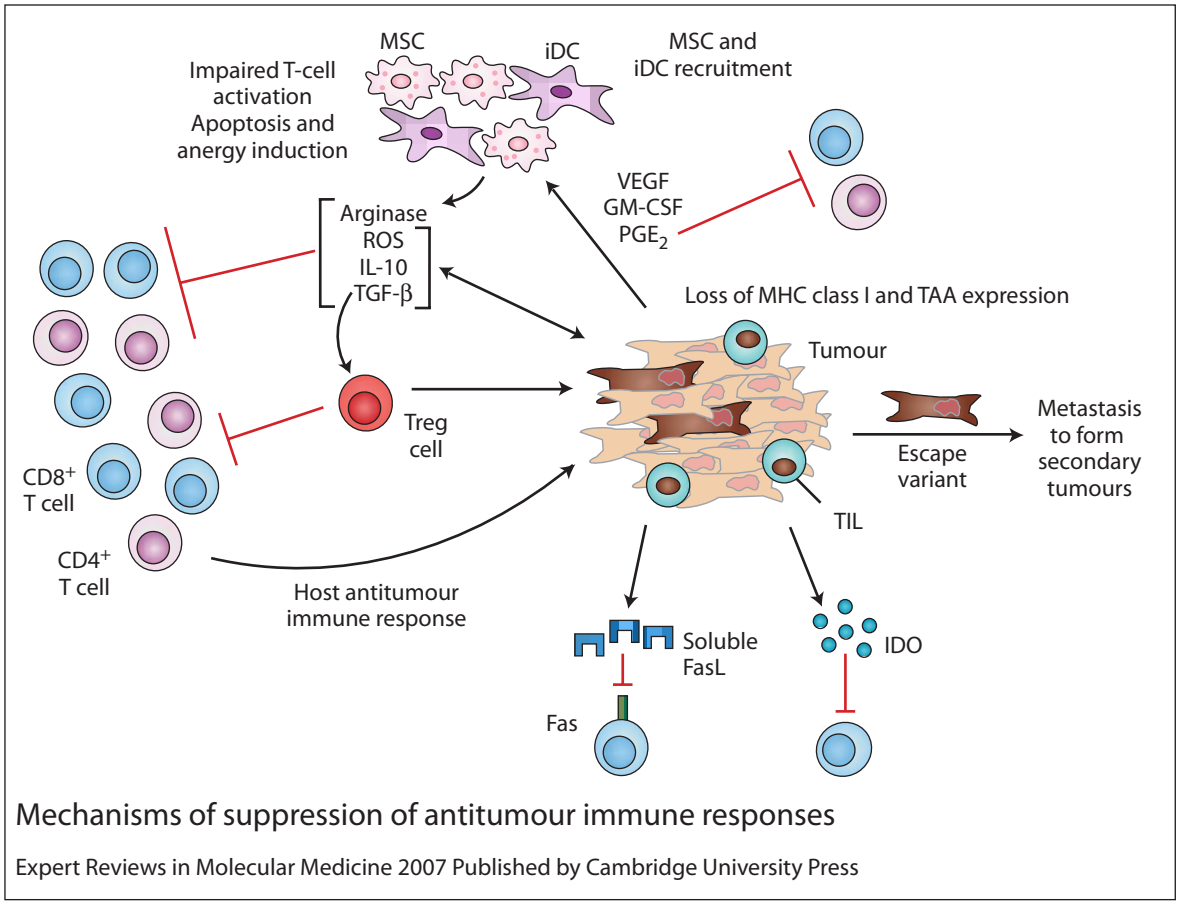


Figure 1. Mechanisms of suppression of antitumour immune responses. The relationship between a tumour and the immune response is dynamic, with immune cells striving to break through immunosuppressive barriers to eliminate the tumour. Various mechanisms can help tumour cells to survive the host antitumour immune response and metastasise. Alterations in tumour-intrinsic molecules, such as loss of MHC class I and TAA expression can prevent immune detection of tumours. Tumours release sFasL, which causes Fas-mediated apoptosis of T cells, and also IDO, which inhibits T-cell function. Tumours can also produce factors including VEGF and GM-CSF that enhance the recruitment of immunosuppressive MSCs and iDCs from the bone marrow. These cells produce factors that impair T-cell activation (e.g. arginase, IL-10) and directly kill T cells (e.g. ROS). MSCs and iDCs also produce TGF-β, which further promotes proliferation of Treg cells, which in turn further inhibit T-cell activation. Although many T cells successfully evade these immunosuppressive mechanisms to infiltrate the tumour (e.g. TILs), once within the mass they often become functionally defective and pro-tumourigenic. Abbreviations: GM-CSF, granulocyte–macrophage colony-stimulating factor; iDC, immature dendritic cell; IDO, indoleamine-2,3-dioxygenase; IL-10, interleukin 10; MHC, major histocompatibility complex antigen; MSC, myeloid suppressor cell; ROS, reactive oxygen species; sFasL, soluble Fas ligand; TAA, tumour-associated antigen; TCR, T-cell receptor; TGF-β, transforming growth factor β; TIL, tumour-infiltrating lymphocyte; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

mutations and angiogenesis. Phagocytosis of apoptotic cells by macrophages has been shown to increase secretion of anti-inflammatory and pro-tumourigenic mediators such as interleukin (IL)-10, PGE_2 and transforming growth factor (TGF)-β (Refs 26, 27), yet decrease the secretion of pro-inflammatory cytokines such as IL-12 (Ref. 28). TGF-β has been shown to promote stromal cells, including macrophages and fibroblasts, to proliferate and secrete angiogenic and tumour proliferative factors such as vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2), through the NF-κB pathway (Refs 29, 30). COX-2 promotes

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proliferation and inhibits apoptosis of tumour cells (Ref. 31). The COX-2 inhibitor celecoxib is currently being utilised in clinical trials for treatment of multiple malignancies including colorectal (Ref. 32) and non-small-cell lung cancer (Ref. 33). TGF-β promotes stromal cells to produce PGE_2 and type 2 cytokines, such as IL-4 and IL-10. Therefore, neoplastic cells can promote their own growth by the secretion of IL-10, IL-4, PGE_2 and TGF-β, which can upregulate the expression of anti-apoptotic genes encoding c-FLIP, Bcl-x_L and Mcl-1 (Refs 34, 35, 36) and angiogenesis activators such as matrix metalloproteinase (MMP)-2 and MMP-9 (Refs 37, 38). TGF-β can also prevent the maturation of DCs, and increased PGE_2 concentration will decrease the expression of major histocompatibility complex class I and II on DCs (Refs 39, 40). These alterations can inhibit the antigen-presenting capabilities of DCs and therefore their ability to activate NK cells and cytotoxic T lymphocytes (CTLs).

Alterations in tumour-associated signalling events, such as constitutive STAT-3 activation (Ref. 41), have been implicated as an important mechanism that underlies several of these immunosuppressive characteristics. Constitutive STAT-3 activity in tumour cells drives the production of cytokines such as IL-10 and VEGF that inhibit pro-inflammatory reactions within the host–tumour microenvironment. This, in turn, impairs DC maturation and activation, resulting in suppression of antitumour T-cell responses. Aberrant STAT-3 signalling might therefore have profound consequences on both innate and adaptive immunity, and strategies that block STAT-3 signalling could restore both antigen-presenting cell function and the generation of antitumour T-cell activity. This has been demonstrated by using dominant-negative or antisense oligonucleotide approaches that impede STAT-3 activity (Ref. 41).

Tumour cells can abnormally secrete the intracellular high-mobility group box 1 (HMGB1) protein, a nuclear DNA-binding protein responsible for the transcriptional activation of many genes in somatic cells (Ref. 42). HMGB1 is released from necrotic cells and binds to RAGE (the 'receptor of advanced glycation end products') to drive innate cell migration and promote inflammatory responses (Ref. 42). Once bound to DNA, HMGB1 has been shown to alter transcription of multiple genes (Refs 43, 44) and promote metastasis (Ref. 45), and is therefore a poor prognosis marker and a good target for therapy.

There are multiple mechanisms or pathways that tumour cells can utilise to thwart the attempts of the host to eradicate them immunologically. Some prominent mechanisms (Fig. 1) will be discussed below.

Mechanisms of immune evasion by the tumour

Considerable effort has been expended in developing immunotherapeutic strategies that aim to promote the activation and expansion of tumour-specific T cells in vivo. Many clinical trials of immunotherapies have been conducted, particularly in melanoma, resulting in higher frequencies of circulating tumour-specific T cells (Refs 46, 47). However, increases in T-cell frequencies were only rarely associated with clinical responses, which suggests that mechanisms other than T-cell priming prevent the generation of an effective antitumour immune response.

The molecular mechanisms by which cancer cells thwart the host immune system have been studied extensively in mouse tumour models and in the clinic. In general, tumours utilise two broad strategies: they either 'hide' from cells of the immune system or they eliminate/compromise the immune cells (Fig. 1). Some of these mechanisms, which may contribute alone or in combination to escape immune attack, include immunoediting, T-cell tolerance or anergy, suppression by regulatory cell populations and the production of soluble factors, inhibitory ligands or enzymes (Refs 48, 49). In preclinical models, there is evidence that, in different settings, disrupting each of these mechanisms can lead to some degree of T-cell-mediated control of tumour growth and a combination of therapies can be even more effective. Which tumours employ what mechanisms is a complex issue, and will probably change over the time course of tumour progression. Table 1 gives a brief summary of several mechanisms whereby tumours can influence host defence networks. For the purposes of this review, we will concentrate on two major regulatory mechanisms: the process by which an immune response functions to enhance tumour progression directly through providing a

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Table 1. Immune evasion strategies for tumour escape[a]

	Mechanism	Refs
Alterations in cell proteins		
MHC class I	Decreased or altered expression; prevents tumour recognition by CTLs	154
Tumour antigens	Antigen shedding or decreased expression; prevents tumour recognition by CTLs	155
Costimulatory molecules	Decreased B7-1 and B7-2 expression; promotes T-cell anergy	156, 157
β_2-Microglobulin	Abnormal MHC/HLA class I antigen presentation; results in defective CTL responses	158
TAP1/TAP2	Abnormal MHC/HLA class I antigen presentation; results in defective CTL responses	159, 160
Inhibitory ligands		
PD-L1/B7-H1	Binds to PD-1 on activated T cells; inhibits T-cell function	161
B7.x/B7-H4	T-cell inhibitory ligand; inhibits T-cell activation	61, 162
CTLA-4	T-cell inhibitory costimulation molecule	151
Tumour-derived factors		
IL-10	Blocks DC priming of CTLs in vitro and GM-CSF-induced DC chemotaxis	163, 164
TGF-β	Inhibits antitumour T cells; increases Treg proliferation in situ; promotes VEGF production by stromal cells	165, 166
GM-CSF	Promotes blood vessel formation for tumour growth; chemoattractant for bone-marrow-derived MSCs	167
PGE_2	Decreases MHC expression by DCs; inhibits cytokine production by $CD4^+$ T cells	168
sFasL	Inhibits Fas-mediated tumour killing by CTLs	169
Arginase	Impairs T-cell activation by downregulation of the CD3ζ chain in the TCR	116, 170
IDO	Suppresses T-cell function by tryptophan depletion and production of proapoptotic metabolites	62
Adenosine	Inhibits tumour-specific CTL activity	171
Inhibitory cell populations		
$CD4^+CD25^+FoxP3^+$Treg	Suppresses activation of CTLs	87, 172
$CD8^+CD45RO^+CCR7^+$Treg	Suppresses activation of T cells by IL-10 production	63

(continued on next page)

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Table 1. Immune evasion strategies for tumour escape[a] *(continued)*

	Mechanism	Refs
$CD11b^{+}Gr1^{+}$MSC	Produces arginase to impair T-cell activation; produces ROS to kill T cells	117, 173, 174
TAM	Produces ROS (NO, H_2O_2), TGF-β and IL-10; promotes T-cell apoptosis	175
iDC	Produces ROS, TGF-β and IL-10; promotes T-cell apoptosis	169

[a]This table summarises a partial list of strategies used by tumour cells to evade immune detection (reviewed by Refs 17, 48, 169).

Abbreviations: CTL, cytotoxic T lymphocyte; DC, dendritic cell; GM-CSF, granulocyte–macrophage colony-stimulating factor; HLA, human leukocyte antigen; iDC, immature dendritic cell; IDO, indoleamine-2,3-dioxygenase; IL-10, interleukin 10; MHC, major histocompatibility complex; MSC, myeloid suppressor cell; NO, nitric oxide; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; sFasL, soluble Fas ligand; TAM, tumour-associated macrophage; TAP, transporter associated with antigen processing; TCR, T-cell receptor; TGF-β, transforming growth factor β; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

selective pressure; and immunosuppression by regulatory cell types, namely T regulatory (Treg) cells and myeloid suppressor cells (MSCs). These cell types are particularly important because they have been documented to suppress host immunosurveillance.

Immunoediting

The theory of cancer immunoediting extends the original concept of immunosurveillance to propose that recognition of abnormal cells by the immune system imposes a selective pressure on developing neoplasms (Ref. 50). That is, as a result of tumour heterogeneity and genetic instability, the eradication of immunogenic or sensitive tumour cells within a mass or lesion by an antitumour response may unintentionally lead to the outgrowth of less immunogenic or more apoptosis-resistant escape variants that possess heightened aggressive behaviour. This leads to malignant progression and metastatic development by tumour escape variants that have evolved mechanisms to circumvent host defences. Therefore, an induced immune response against a tumour can have both positive and negative consequences on cancer progression. The outgrowth of antigen-loss variants in patients who have responded to treatment with vaccines (Refs 51, 52) or following adoptive transfer of T cells (Ref. 53) is consistent with the concept of immunoediting. Indeed, other therapies, such as irradiation and chemotherapy, have the potential to select for more therapy-resistant tumours. A further molecular understanding of these escape variants may identify potential targets for therapeutic intervention and explain, at least in part, disease recurrence.

Studies by Schreiber and colleagues (Refs 54, 55, 56) have provided seminal insights into the mechanistic basis of immunoediting. It has become evident that the production of interferon (IFN)-γ plays a crucial role in immune selection. Much of this effect appears to be intrinsic to the tumour cells (Refs 56, 57), with several human tumours demonstrating genetic mutations that result in defective IFN-γ signalling (Ref. 58). Normally the immunogenicity of tumours can be enhanced following exposure to IFN-γ. Activated T cells and NK cells produce IFN-γ, which allows these effector cells to eliminate those tumour cells that are most responsive to the IFN-γ-mediated effects. Tumour cells that are less responsive will be potentially less immunogenic and more tumourigenic; therefore, the mass that emerges has been immunologically 'edited' and selected for more-aggressive behaviour.

IFN-γ can also have negative consequences as the cytokine has been shown to induce expression of programmed death receptor ligand 1 (PD-L1; also called B7-H1) on the surface of tumour cells (Ref. 59). B7-H1 induces apoptosis of T cells (Ref. 60), and also inhibits

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the function of T cells and DCs (Ref. 59). Some of the suppressive functions of B7-H1 are mediated by the receptor PD-1 on the surface of activated T cells and myeloid cells, whereas other functions may be independent of PD-1 (Ref. 59). B7-H4, also known as B7.x, has been shown to inhibit antitumour responses by arresting T-cell proliferation and inhibiting cytokine secretion by interfering with costimulation (Ref. 61). IFN-γ signalling has also been shown to induce indoleamine-2,3-dioxygenase (IDO) production by DCs to catabolise tryptophan; this has several deleterious consequences including functional inhibition and/or deletion of T cells (Ref. 62). In addition to changes in tumour cells that render them invisible to immune attack or recognition, tumours can recruit or activate negative regulatory immune cells, including Treg cells and MSCs that suppress antitumour immune responses.

Treg cells

Treg cells can be subdivided into $CD4^+$ and $CD8^+$ subsets. Tumour-associated $CD8^+CD45RO^+CCR7^+$ T cells have been shown to produce IL-10 and suppress T-cell activation, whereas $CD8^+CD45RO^+CCR7^+$ T cells from the blood neither produce IL-10 nor suppress T-cell activation (Ref. 63). Further studies are needed to characterise the cells and their role in tumour immune evasion. $CD4^+$ Treg cells can be divided into three populations: $CD4^+CD25^+FOXP3^+$ (Treg) cells, $CD4^+IL\text{-}10^+FOXP3^-$ (Tr1) cells (Ref. 64) and $CD4^+TGF\text{-}\beta^+$ (Th3) cells (Ref. 65). This review will focus on Treg cells, which have clearly been shown to play a role in tumour progression.

Treg cells are naturally occurring $CD4^+$ T cells that act to inhibit autoimmune responses and have been implicated in the suppression of antitumour immunity. Although CD25 (IL-2R) and FoxP3 molecules have been used for the identification of Treg cells in mice, the situation in humans is more complicated (Refs 66, 67). Because of the constant exposure of humans to foreign antigens, there is always some level of circulating effector cells that express CD25, which is a marker of cell activation. FoxP3 may be induced in activated human cells so it is also not an ideal identifier of Treg cells (Refs 68, 69, 70). In the human setting, Treg cells are best defined by their suppressive function, which makes their study difficult. The $CD4^+CD25^{high}FoxP3^+$ phenotypic markers usually identify Treg cells but definitive identification is based on functional characteristics, including their anergic state and inability to proliferate in response to in vitro stimulation. They can also be identified by their ability to actively suppress $CD4^+CD25^-$ T cells, $CD8^+$ T cells, DCs and NK cells in a cell-to-cell contact-dependent manner, although this mechanism of action has not been confirmed in vivo (Refs 71, 72, 73, 74).

Increased numbers of Treg cells have been observed in the peripheral blood of patients with many types of cancer, including breast and pancreatic cancer (Ref. 75), malignant melanoma (Ref. 76), head and neck cancer (Ref. 77) and hepatocellular carcinoma (Ref. 78). In patients with gastric and oesophageal carcinomas, increased numbers of Treg cells in the peripheral blood were shown to drop following resection, whereas the numbers of Treg cells increased again in patients who relapsed (Ref. 79). Increased numbers of Treg cells have also been described in haematological malignancies such as lymphomas (Refs 80, 81), acute myeloid leukaemia (Ref. 82), multiple myeloma (Ref. 83) and chronic lymphocytic leukaemia (CLL), which demonstrates a stage-dependent increase in $CD4^+CD25^{high}FoxP3^+CTLA\text{-}4^+GITR^+$ Treg cells with suppressive capability (Ref. 84). In addition, Treg cells accumulate at the tumour site in multiple cancers such as non-small-cell lung carcinoma (Ref. 85), ovarian cancer (Ref. 86) and hepatocellular carcinoma (Ref. 78).

There is mounting evidence that Treg cells can inhibit host antitumour responses. In mice, it has been demonstrated that anti-CD25 treatment enhances the efficacy of tumour vaccines, including the development of long-term memory responses (Ref. 87). In addition, removal of Treg cells has been shown to elicit antitumour immunity against established tumours in murine model systems (Refs 88, 89). In an adoptive immunotherapy model of melanoma, transfer of $CD4^+CD25^+$ Treg cells effectively prevented tumour control by $CD8^+$ T cells (Refs 88, 89). Increased frequencies of Treg cells have also been shown to be inversely correlated with survival in patients with gastric carcinoma (Refs 90, 91) and ovarian cancer (Ref. 86), and increased Treg cell numbers are correlated with advanced disease and unfavourable cytogenics in patients with CLL

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(Ref. 84). There is also evidence that Treg cells specific for tumour antigens exist in cancer patients and are capable of suppressing TAA-specific effector cells (Ref. 87) and Treg cells from lung cancer patients have been shown to be capable of inhibiting T-cell responses (Ref. 85). Together, the human and mouse data strongly suggest that Treg cells are a major impediment to establishing an effective antitumour immune response.

Because of the evidence that Treg cells prevent the development of antitumour immunity in patients with cancer, investigators are attempting to decrease the number and function of these cells. One possible approach involves the use of human anti-Tac (anti-CD25) antibody or denileukin diftitox (DAB(389)IL-2, ONTAK®, a fusion protein comprising a diphtheria toxin and an IL-2 moiety that specifically targets $CD25^+$ tumour cells). However, these treatment modalities have the potential to inhibit activated effector cells, which also express CD25 (Refs 92, 93, 94). DAB(389)IL-2 has also been used to eliminate $CD25^{high}$-expressing Treg cells selectively without inducing toxicity on cells expressing lower levels of CD25. DAB(389)IL-2 reduces significantly the number and immunosuppressive function in vivo of Treg cells in the peripheral blood of patients with metastatic renal cell carcinoma (Ref. 95). In mice, both cyclophosphamide and 5-fluorouracil treatment have been shown to augment antigen-specific T-cell responses and tumour control through the depletion of Treg cells (Refs 96, 97, 98, 99, 100), indicating that chemotherapeutic regimens may be used to enhance the development of antitumour immune responses. An experiment in patients with CLL treated with fludarabine demonstrated that chemotherapy could lead to both decreased numbers and impaired function of Treg cells (Ref. 84). An alternative therapeutic approach is to decrease the number of Treg cells at the site of the tumour by preventing the trafficking of these cells into the tumour. It has been shown that the chemokine CCL22 produced by the tumour can attract $CCR4^+$ Treg cells into the tumour microenvironment and that antibodies against CCL22 prevented the accumulation of Treg cells at the tumour site (Ref. 86).

It is also important to recognise that treatment of patients might lead to increased numbers of Treg cells, which could interfere with the effectiveness of therapies. For example, IL-2 treatment has been shown to result in an expansion of Treg cells in both healthy and lymphopaenic patients with either melanoma or renal cell carcinoma (Refs 101, 102, 103). DC vaccination of patients with melanoma also led to an increase in the number of Treg cells (Refs 101, 102, 103).

MSCs

Another strategy by which tumours downregulate antitumour immunity is through the induction of a population of immature myeloid cells, termed MSCs. In mouse tumour models, MSCs are characterised by the expression of Gr1 and CD11b cell-surface markers and consist of a heterogeneous population of cells that include immature DCs, macrophages and granulocytes (Refs 104, 105). Human MSCs are mostly $CD34^+$ and are prevalently of the immature phenotype $CD34^+CD33^+CD13^+$. MSCs have been shown to exist in numerous animal models (Ref. 106) and in patients with a variety of cancers including head and neck (Ref. 107), breast (Ref. 108) and colon (Ref. 109) carcinoma. In the presence of tumour, normal haematopoiesis is dysregulated, leading to the accumulation of this immature population of myeloid cells at the site of tumour and within the blood and primary and secondary lymphoid organs. These cells are thought to be recruited from the bone marrow to the tumour by the release of tumour-derived soluble factors, whereas other factors have been found to modulate the MSCs to perform immunosuppressive functions, thus contributing to tumour progression. There is also a correlation between the expansion of the MSC populations and the presence of immune suppression both in animal models and in patients with cancer.

Many tumour types have been shown to recruit MSCs through the production of several tumour-derived factors such as VEGF, TGF-β, IL-6, IL-10, colony-stimulating factor (CSF)-1 and granulocyte–macrophage colony-stimulating factor (GM-CSF) (Ref. 110). MSCs have been reported to suppress the activation of both systemic and tumour-specific $CD4^+$ and $CD8^+$ T cells (Refs 111, 112). They also produce high levels of the inhibitory enzyme arginase I, stimulated by the anti-inflammatory cytokines

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IL-10 and TGF-β (Ref. 113). Arginase I converts the amino acid L-arginine to the compounds ornithine and urea, which themselves can inhibit T-cell function. Nitric oxide synthase (NOS) is also produced by MSCs, and this metabolises L-arginine to nitric oxide and hydroxide. These resulting ROS are responsible for directly inhibiting T-cell function and leading to T-cell apoptosis (Refs 114, 115, 116). Because many human tumours contain cells of the myeloid lineage, strategies that deplete or offset the inhibitory effect of MSCs have been considered for therapeutic modalities. It has been demonstrated in mouse tumour transplant models that depletion of myeloid cells by anti-Gr1 monoclonal antibody had a therapeutic effect (Ref. 117). However, Gr1 is also expressed on other cell types, particularly neutrophils, which if depleted, may increase the incidence of opportunistic infections. Differentiation of MSCs into functional antigen-presenting cells can also reduce their suppressive functions. This has been achieved with some degree of success by administration of all-*trans*-retinoic acid (ATRA), IFN-γ and vitamin D3 (Refs 118, 119, 120). Pharmacological inhibition of the MSC suppressive pathways involving NOS and arginase also represent promising targets for overcoming MSC-induced immunosuppression and is currently being explored (Refs 110, 121).

Preclinical modelling of cancer progression

Animal models are an essential preclinical tool in the study of the molecular mechanisms of cancer and in the development and testing of new antitumour therapies, before moving into a complex clinical environment. The relevance of the model depends on how closely it resembles the human disease condition in its development, histology, pathology, response to therapy and progression, and particularly in its progression to metastases. Metastatic occurrence, as discussed earlier, is a major determinant of clinical outcome and patient survival, and is therefore an important target in the development of systemic therapies. However, the majority of mouse cancer models do not routinely metastasise or do not metastasise with the same organ-specific dissemination pattern as the human tumour type. The most commonly used preclinical animal is the mouse, as a result of extensive background knowledge and the ability to develop inbred populations with known genomics and biochemical and immunological characteristics. Mice are also easy to maintain, but differ to humans in some of their carcinogenesis processes and rates of metabolism (Refs 122, 123). Various mouse model systems have been developed including tumour transplant and transgenic models of tumour growth, progression and metastasis. Because differences exist in the transformation and oncogenesis between humans and mice, the development of new and improved (more relevant) preclinical mouse models might require humanisation before becoming clinically relevant (Refs 124, 125). Preclinical models that recapitulate the chronic nature of host–tumour interactions are required to understand better the complexity and dynamic nature of these interactions. Below we discuss some of the advantages and limitations of these mouse models in preclinical studies.

Tumour implant models in syngeneic immunocompetent mice

Tumour transplant models make use of tumour cells or tumour cell lines that are implanted into syngeneic mice, usually subcutaneously but sometimes orthotopically, intraperitoneally, or intravenously to establish experimental lung metastases. The rapid and predictable progression of tumour growth makes this an attractive experimental system, and has been used extensively in the development and testing of new therapies. An appreciation of therapeutic efficacy, particularly immunotherapies, in preclinical models usually requires long-term host–tumour interactions, which is often lacking in these tumour transplant models because of their rapid growth kinetics. It is also important to point out that tumour cell lines used in these models have probably already been selected for a predetermined tumourigenic phenotype and therefore do not necessarily interact with the host in the same way as a developing autochthonous tumour and might respond differently to therapeutic agents (Refs 126, 127). Additionally, these models do not recapitulate the genetic complexity of human tumour development and frequently do not spontaneously metastasise, and when they do, the pattern of dissemination and the response to therapy does not necessarily mirror the human tumour type. However, these tumour models do

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have the advantage of taking place in a syngeneic system where the tumour and the host stroma are from the same species. Lastly, tumour transplant models probably elicit an acute immune response, which contrasts with an autochthonous tumour growth setting where tumours develop in an environment of more-chronic host–tumour interactions, and in the presence of an intact immune system, which includes many homeostatic mechanisms that could influence the immunoediting of the resultant tumour masses. Nonetheless, syngeneic mouse tumour transplant models are easy to use and provide rapid experimental results. They also have an intact immune system and the tumour cell challenge and stromal cells are of the same species. These characteristics continue to make this an appealing experimental system to study various questions and to provide preliminary preclinical data.

Orthotopic xenograft models

Models based on xenotransplantation of human tumour cells or tumour cell lines into immunodeficient (nude) mice share some of the characteristics and raise some of the concerns as discussed above for syngeneic tumour models. However, these models do allow the direct investigation of human tumour cell responses to therapeutic strategies in vivo. Orthotopic implantation of human tumour cells, rather than heterotopic (e.g. subcutaneous) tumour challenges, results in a pattern that more closely resembles the clinical behaviour of that particular human tumour type (Refs 128, 129). However, differences in disease progression may occur as a result of the difference in species between mouse stromal cells and the human tumour (Ref. 130). Orthotopic xenotransplantation has shown utility in evaluating in vivo tumour responses to some forms of therapy, although not immunotherapies owing to the immunodeficient state of the host. Although these orthotopic xenograft models continue to be routinely used as preclinical models in the evaluation of drugs, their lack of correlation with clinical response also raises questions about their translational relevancy (Refs 131, 132). Because these models use human tumour cells or tumour cell lines that have already been 'selected' for their tumourigenicity, they are not appropriate to study early tumourigenesis, their response to various antitumour agents or the influence of the host immune response in this process (Refs 133, 134, 135).

Transgenic models of autochthonous tumour development

Genetically modified mice that result in autochthonous tumour development and progression have become important tools in the study of the molecular mechanisms involved in tumour initiation and progression, and have shown a promising recapitulation of the tumourigenic process in terms of human disease markers and events (Ref. 136). Innovative methods have been developed to target oncogene expression to specific tissue sites, for example use of the mouse mammary tumour virus (MMTV) promoter to target gene expression in mammary tissue (Ref. 137). Tissue targeting can also be combined with gene expression control technology, which permits the activation or inactivation of gene function in a time-specific manner. Therefore, models can be developed that have tumours arising in situ, only in targeted tissues and within a specified time frame, although many human tumour types do not yet have a related genetically modified mouse model. A major advantage in many of the transgenic models over tumour transplant models is the protracted nature of disease progression and in some cases the development of metastatic disease. Development of metastases is still usually less aggressive and affects fewer sites than many human tumours, but is a good foundation for further humanisation of these models (Refs 124, 125). Long-term transgenic models allow for the testing of extended therapy or combination strategies and their effects on systemic disease in the context of an intact and functional immune system. Given the chronic nature of host–tumour interactions, it also allows for the long-term study of these interactions and their influence on tumour development and progression.

Immunotherapy strategies

Over the years there have been numerous immunotherapeutic strategies tested, starting with the use of the bacterial vaccine Coley's toxin at the beginning of the 20th century (discussed in Ref. 138). Immunotherapies can be divided into two broad categories: (1) active immunisation through vaccination, which requires the stimulation of host antitumour

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responses; or (2) passive immunisation by transferring tumour-specific T cells or antibodies. To be most effective, these forms of immunotherapy require that the host be immunocompetent and possess a supportive environment for the continued function of antitumour T cells (induced or transferred). A pre-existing antitumour immune response has been identified in numerous disease settings, such as tumour-specific antibody titres (Ref. 139) and tumour-specific CTLs (Refs 140, 141), which can potentially be enhanced. Because immunotherapies work by activating the immune response of the host, a crucial issue is the immune status of the tumour-bearing individual during the administration of immunotherapy. Both active and passive forms of cancer therapy will probably have the greatest chance of success when administered in a minimal disease setting and in combination with a reduction or elimination of tumour-induced immunosuppression that will allow the persistence of antitumour responses.

The most direct and effective method for eliminating tumour-induced immunosuppression is to remove or eradicate the tumour cells (Ref. 142). Many primary tumours can be surgically resected; however, residual tumour cells are still likely to persist as metastases or undetectable micrometastatic deposits. Eradication of these residual tumour cells has proven difficult with conventional (chemotherapy and radiation) therapies owing to the ability of tumour cells to develop resistance to therapeutic regimens and to disseminate throughout the body. The nature of metastatic disease therefore lends itself to the use of immunotherapeutic strategies that exploit the natural immune defence mechanisms of the host to detect and destroy tumour cells. Therefore, a combination of both conventional and immunotherapeutic strategies might ultimately prove more effective against residual disease. Conventional therapies can act as an adjuvant for immunotherapies by promoting tumour cell death, which may then tip the balance towards an antitumour pro-inflammatory response and provide a source of antigen for the activation of T cells through cross-priming by DCs. Because residual tumour load, at least initially following resection, will be lower, this should allow an immunotherapy-induced immune response the opportunity to eradicate residual tumour before immunosuppressive networks can be re-established leading to further tumour progression. Establishing or enhancing a patient's state of 'immunosurveillance' may be a particularly effective method for controlling metastatic progression after removal of a primary tumour and when there is minimal residual disease.

Although several clinical trials have incorporated immunotherapeutic strategies, the actual clinical response rate has been low (Ref. 141). Failure of these therapies could be due, in part, to the reality that most trials are conducted in patients with advanced disease who have already failed prior standard of care treatments. These patients may have too extensive a tumour burden for an immunotherapeutic strategy to overcome the many tumour-induced mechanisms of suppression or evasion. As stated earlier, it is likely that a combination of conventional and experimental immune-based therapies will be required to have a better antitumour effect. The transfer of autologous tumour-specific T cells expanded ex vivo has also shown promising results when combined with a lymphodepletion chemotherapeutic regimen (Refs 143, 144). It is not entirely clear why lymphodepletion enhances the effect of T-cell adoptive transfer. It is possible that following clinically induced lymphopaenia, lymphocyte numbers are restored through endogenous homeostatic mechanisms, which increases transferred cell numbers and survival; or that negative regulatory cells are eliminated with the depletion, thus allowing the enhanced survival or function of the transferred cells.

Cytokines have been shown to play a key role in regulating lymphocyte survival and expansion; indeed, several, including IL-2, IL-7, IL-12, IL-15 and IL-21, are being tested in immunotherapy protocols (Ref. 145) to enhance T-cell effector function and survival. Certain cytokines protect T cells through receptor-mediated anti-apoptotic signals (Ref. 146), promote T-cell proliferation and survival (Ref. 147) or maintain memory cell populations (Ref. 148). However, it has become clear that stimulation of an antitumour response is insufficient to overcome tumour escape mechanisms and to elicit durable cancer regression (Ref. 141). Therefore, blockade of negative regulatory mechanisms on T cells, such as CTLA-4, may be required to improve

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therapeutic efficacy further (Refs 149, 150, 151). Anti-CTLA-4 antibody treatment has been used alone or in combination with other treatments to affect tumour growth (Refs 152, 153). Because each tumour type might express various antigens and develop different immunosuppressive mechanisms that could change with tumour progression, the timing of some forms of immunotherapy may also become relevent. Monitoring the appearance of immunosuppressive mechanisms, possibly by biomarker assessments, may thus become important for tailoring the nature and timing of therapeutic strategies.

Therefore, for the greatest efficacy, a combination of therapies based on the nature of the disease should be combined to affect tumour cells directly (e.g. radiation and chemotherapy), enhance the resident antitumour immune responses and inhibit the mechanisms of immune suppression. Continued investigations that characterise tumour escape mechanisms and immunosuppressive networks, and approaches to monitor their development, will therefore become important in developing better immunotherapies that achieve higher rates of longer lasting clinical responses.

Clinical implications and applications

Increased understanding of the molecular changes that occur during tumour progression will allow us to identify potential antitumour targets for therapeutic interventions. Host–tumour interactions are complex and ever changing, with the immune response 'editing' the tumour and extrinsic tumour-mediated activities affecting the immune response. It is likely that treatment strategies that take into account the molecular characteristics of the tumour type of the host and the occurrence of immunosuppressive mechanisms will permit better therapeutic efficacy. Given the nature of metastatic disease, immunotherapies seem particularly well suited for the treatment of this disseminated disease state.

During neoplastic progression, tumour cells can be stimulated to proliferate by pro-inflammatory mechanisms at the same time that immune cells are suppressed by anti-inflammatory mechanisms. Therefore, treatments that incorporate either pro- or anti-inflammatory modalities may prove a 'double-edged sword' in treating cancer. A detailed understanding of these interactions will allow the manipulation of host defences for the development of more efficacious antitumour therapies.

Preclinical models that mimic human disease progression will improve our understanding of the complex and chronic nature of host–tumour interactions and the identification of potential therapeutic targets. Following the development of new therapies, more relevant animal models are also needed to guide clinical trial design and predict clinical outcomes.

Concluding remarks

Although there is great promise in the use of immunotherapies for the treatment of neoplastic disease, characterisation of tumour escape mechanisms and an understanding of the complex nature of host–tumour interactions are crucial for the objective of improving antitumour therapies and clinical outcome. As our knowledge of these interactions increases and technical advances allow us to monitor the characteristics of disease progression better, the determination of appropriate immunotherapy strategies or combinations may ultimately lead to improved outcomes for patients.

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A basic immunology text that covers possible immunotherapy strategies and prospects for their future:

Janeway, C.A., Jr, Travers, P., Walport, M. and Shlomchik, M. (2001) Immunobiology: The Immune System in Health and Disease (5th edn), Garland

A text that covers a broad range of cancer topics, including cancer immunology (Section 2), therapies (Sections 9, 11, 12) and biotherapeutics (Section 13):

Kufe D. et al. (eds) (2003) Cancer Medicine 6, BC Decker

Nature Reviews Cancer and Nature Reviews Immunology have covered topics that include host–tumour interactions, regulatory T cells, tumour microenvironment and suppressive networks.

Seminars in Cancer Biology covers a different topic of molecular oncology in each issue and is a good source of in-depth reviews on specific topics relating to cancer biology. Available to subscribers of the IDEAL Library or Science Direct:

http://www.sciencedirect.com/science/journal/1044579X

The National Cancer Institute provides an online information service run for members of the public and professionals in the field of oncology. It contains numerous links to other cancer-related resources and includes cancer epidemiology, treatments, screenings, terminology, genetics and support services:

http://www.cancer.gov/

The National Institutes of Health provides a database for patients and members of the public with current information about clinical research studies, including those involving immunotherapies:

http://www.clinicaltrials.gov/

Features associated with this article

Figure
Figure 1. Mechanisms of suppression of antitumour immune responses.

Table
Table 1. Immune evasion strategies for tumour escape.

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