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FOXA1 in breast cancer

Harikrishna Nakshatri[1,*] and Sunil Badve[2]

Breast cancer is a heterogeneous disease and classification is important for clinical management. At least five subtypes can be identified based on unique gene expression patterns; this subtype classification is distinct from the histopathological classification. The transcription factor network(s) required for the specific gene expression signature in each of these subtypes is currently being elucidated. The transcription factor network composed of the oestrogen (estrogen) receptor α (ERα), FOXA1 and GATA3 may control the gene expression pattern in luminal subtype A breast cancers. Breast cancers that are dependent on this network correspond to well-differentiated and hormone-therapy-responsive tumours with good prognosis. In this review, we discuss the interplay between these transcription factors with a particular emphasis on FOXA1 structure and function, and its ability to control ERα function. Additionally, we discuss modulators of FOXA1 function, ERα–FOXA1–GATA3 downstream targets, and potential therapeutic agents that may increase differentiation through FOXA1.

Epithelial cells in the normal breast can be phenotypically and functionally subdivided into multiple types, with each subtype expressing unique genes and representing cells at different levels of differentiation (Refs 1, 2, 3). Phenotypic classification has mostly relied on the expression pattern of select surface molecules; only a few key signalling molecules that bestow the phenotype have been characterised (Refs 2, 3). These key molecules are likely to be involved in regulating a gene expression programme for maintaining the phenotype or triggering differentiation of cells. Characterisation of such molecules is therefore critical for understanding normal breast development as well as breast cancer. In this context, the forkhead family transcription factor FOXA1 has generated considerable interest because of its role as a critical component in the hormonal signalling network required for the growth and differentiation of a specific subtype of breast epithelial cells (Refs 4, 5, 6). In this review, we first describe general aspects of FOXA1 and then relate its function to a specific subtype of luminal epithelial cells of the breast and in breast cancer.

A brief history of FOXA1/HNF3α

Hepatocyte nuclear factor 3α (HNF3α) was initially identified as the transcription factor required for high-level expression of transthyretin and

[1]Departments of Surgery, Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

[2]Department of Pathology and Internal Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

*Corresponding author: Harikrishna Nakshatri, R4-202, Indiana University School of Medicine, 1044 West Walnut Street, Indianapolis, IN 46202, USA. Tel: +1 317 278 2238; Fax: +1 317 274 0396; E-mail: hnakshat@iupui.edu

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α_1-antitrypsin in the liver (Ref. 7). Response elements in the regulatory regions of these genes were used to generate DNA affinity chromatography columns for purification of HNF3α from rat liver and its subsequent cloning (Ref. 8). Screening of cDNA libraries with HNF3α cDNA as a probe under low-stringency hybridisation conditions allowed cloning of two additional members of the family: HNF3β and HNF3γ (Ref. 9). Based on the homology of these proteins to *Drosophila* forkhead proteins, HNF3α, HNF3β and HNF3γ were renamed as FOXA1, FOXA2 and FOXA3, respectively (Ref. 10). Obviously, initial functional studies of these genes were focused on their role in the development of the liver (Ref. 10). Binding sites for these transcription factors were found in hundreds of genes encoding gluconeogenic and glycolytic enzymes (Ref. 10). Genetic analysis in mice revealed an important role for FOXA1 in proglucagon expression in the pancreas, FOXA2 in the development of foregut endoderm from which liver and pancreas arise, and FOXA3 in the induction of gluconeogenic enzymes during fasting (Ref. 10). Subsequent studies revealed their role in differentiation of epithelial cells and longevity (Refs 11, 12). The unique ability of FOXA family transcription factors to bind to target sites in silent chromatin in a dominant manner and initiate regulatory events distinguishes them from the rest of the transcription factors (~2000) in the mammalian genome (Ref. 13); therefore, these transcription factors are dubbed 'pioneer factors'.

The FOXA1 regulatory circuit

DNA binding and transactivation

FOXA1 binds to target DNA sequences as a monomer, using a helix–turn–helix motif of ~110 amino acids (Refs 14, 15). This DNA-binding domain is flanked on either side by 'wings' of polypeptide chain that determine the stability of DNA binding (Ref. 15). The DNA-binding domain and the wings bind to the consensus sequence A(A/T)TRTT(G/T)RYTY. While the DNA-binding domain makes contact with the major groove (underlined sequence), the wings make contact with the minor groove of the DNA (sequences adjacent to the underlined sequences). The wings interact more tightly with high-affinity binding sites compared with low-affinity binding sites (Ref. 15). The genome-wide distribution patterns of low-affinity and high-affinity binding sites and the impact of differential binding on target gene expression are yet to be determined.

FOXA2 but not FOXA1 has been analysed extensively for transactivation domains; however, based on sequence conservation, the same regions in FOXA1 as in FOXA2 may also function as transactivation domains (Ref. 16) The N-terminus and the C-terminus both contain transactivation domains (Fig. 1). The N-terminal transactivation domain of FOXA2 is phosphorylated by casein kinase 1 (CK1) and the phosphorylatable amino acid is conserved between FOXA1 and FOXA2 (Ref. 16). Although this phosphorylation is not required for the transactivation function of FOXA2, similar evaluation of CK1 phosphorylation on FOXA1 function has not been performed. In fact, there are no reports on post-translational modifications of FOXA1 and the effect of such modifications on its ability to bind silent chromatin.

Two orphan nuclear receptors – apolipoprotein regulatory protein 1 (ARP-1; also called chicken ovalbumin upstream transcription factor II, COUP-TFII) and small heterodimer partner (SHP; also called NR0B2) – inhibit the transactivation function of FOXA1 (Refs 17, 18). By contrast, androgen receptor (AR), another nuclear receptor, interacts with the DNA-binding domain of FOXA1 and this interaction leads to increased expression of target genes (Ref. 19). FOXA1 also associates with the NK2 homeobox (NKX2.1) transcription factor, leading to repression of genes with the NKX2.1-binding site but lacking a FOXA1-binding site (Ref. 20). However, FOXA1 and NKX2.1 additively activate transcription of genes with both FOXA1- and NKX2.1-binding sites (Ref. 20). The effect of NKX2.1 on transcription of genes with only the FOXA1-binding site is unknown. SMAD family member 3 (SMAD3) transcription factor, which is activated by transforming growth factor β (TGF-β), associates with FOXA1 and prevents FOXA1 from interacting with NKX2.1 and subsequently with DNA (Ref. 21). The C-terminal region of FOXA1 associates with transducin-like enhancer of split 3 (TLE3; also called Groucho-related protein 3, GRG3) and recruits it to chromatin (Ref. 22) (Figs 1 and 2). The FOXA1–TLE3 association on chromatin results in the formation of locally closed chromatin and repression of FOXA1 target genes. Other coregulatory proteins that are essential for the transactivation function

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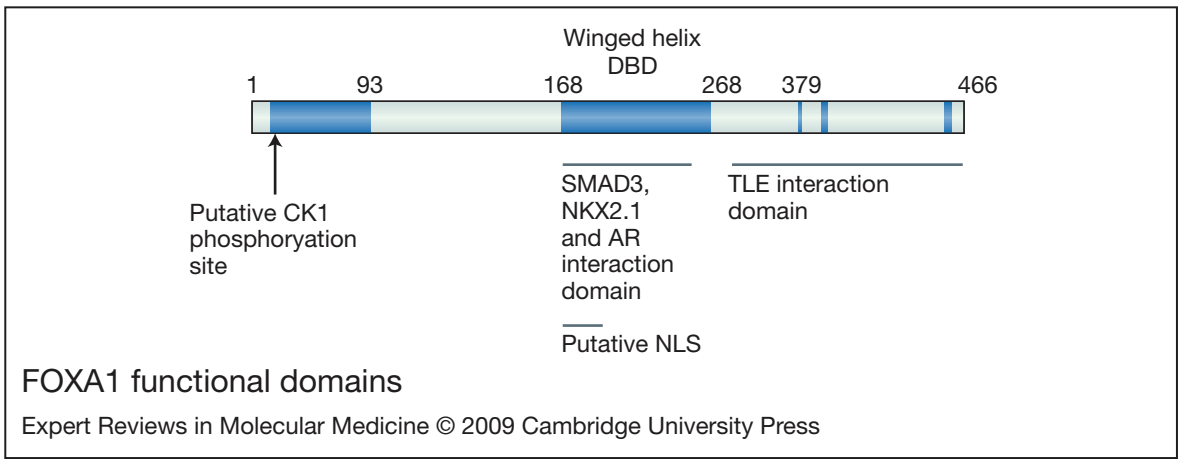


Figure 1. FOXA1 functional domains. The schematic of the FOXA1 polypeptide chain indicates the winged helix–turn–helix DNA-binding domain ('winged helix DBD') and two transactivation domains (TADs). SMAD family member 3 (SMAD3), NK2 homeobox transcription factor (NKX2.1) and androgen receptor (AR) interact with the DNA-binding domain of FOXA1 (Refs 19, 20), whereas TLE3/GRG3 (transducin-like enhancer of split 3/Groucho-related protein 3) associates with the C-terminal TAD (Ref. 22). The casein kinase 1 (CK1) phosphorylation site (at amino acid 18) and the nuclear localisation signal (NLS) have been characterised for FOXA2 and the corresponding amino acids are present in FOXA1 (Ref. 16). Blue bars indicate highly conserved domains; numbers indicate amino acid positions.

of FOXA1 are yet to be identified. It is likely that the ability of FOXA1 to open silent chromatin is dependent on the corecruited positive and negative coregulatory proteins. These coregulatory proteins may impart cell-type specificity to FOXA1 function.

Regulation of FOXA1 DNA binding through histone modification

The DNA recognition element for FOXA1 lacks a GC-rich sequence; thus, DNA methylation is not likely to play a role in restricting FOXA1 binding to DNA within chromatin. Epigenetic modifications of histones involving specific modifications of amino acids in histone tails is another mechanism that dictates binding affinity and/or accessibility of transcription factors to DNA within chromatin (Ref. 23). Accessibility to such DNA is not a regulatory mechanism for FOXA1 as it can bind to silent chromatin (Ref. 13), but binding affinity may be regulated by specific chromatin modifications. This possibility has recently been addressed through genome-wide FOXA1-binding site analysis in MCF-7 breast cancer cells (Ref. 24). In these cells, 12 904 motifs bound FOXA1, representing only 3.7% of sites harbouring FOXA1-recognition motifs. FOXA1 recruitment correlated with methylation of histone H3 lysine 4 (H3K4) (Ref. 24). H3K4 undergoes mono-, di- or tri-methylation and these methylation events are associated with active transcription (Ref. 25). The majority of FOXA1-binding sites displayed H3K4 mono- or di-methylation (Ref. 24). It thus appears that FOXA1 binds to both silent and actively transcribed regions of chromatin; the effect of FOXA1 binding on transcription depends on corecruitment of TLE proteins to chromatin (silencing) or histone H3K4 methylation status around the binding site (activation) (Fig. 2).

The binding of FOXA1 to chromatin regions with H3K4 mono- or di-methylation indicates that the expression levels of enzymes that control mono- or di-methylation of H3K4 will influence the binding affinity of FOXA1 to DNA within chromatin. FOXA1 is not required for these histone modifications (Ref 24). Mixed-lineage-leukaemia proteins MLL1–MLL4, set-domain-containing proteins SET1 and SET9, and ASH1 ('absent, small or homeotic') methylate H3K4 (Ref. 23). Several demethylases are known: histone demethylase lysine-specific demethylase 1 (LSD1; also called BHC100) demethylates mono- and di-methylated H3K4 (Ref. 23); retinoblastoma binding protein 2 (RBP2) demethylates tri- and di-methylated H3K4 (Refs 26, 27); X-linked mental retardation gene SMCX/JARID1C demethylates tri-methylated H3K4 to di- or mono-methylated

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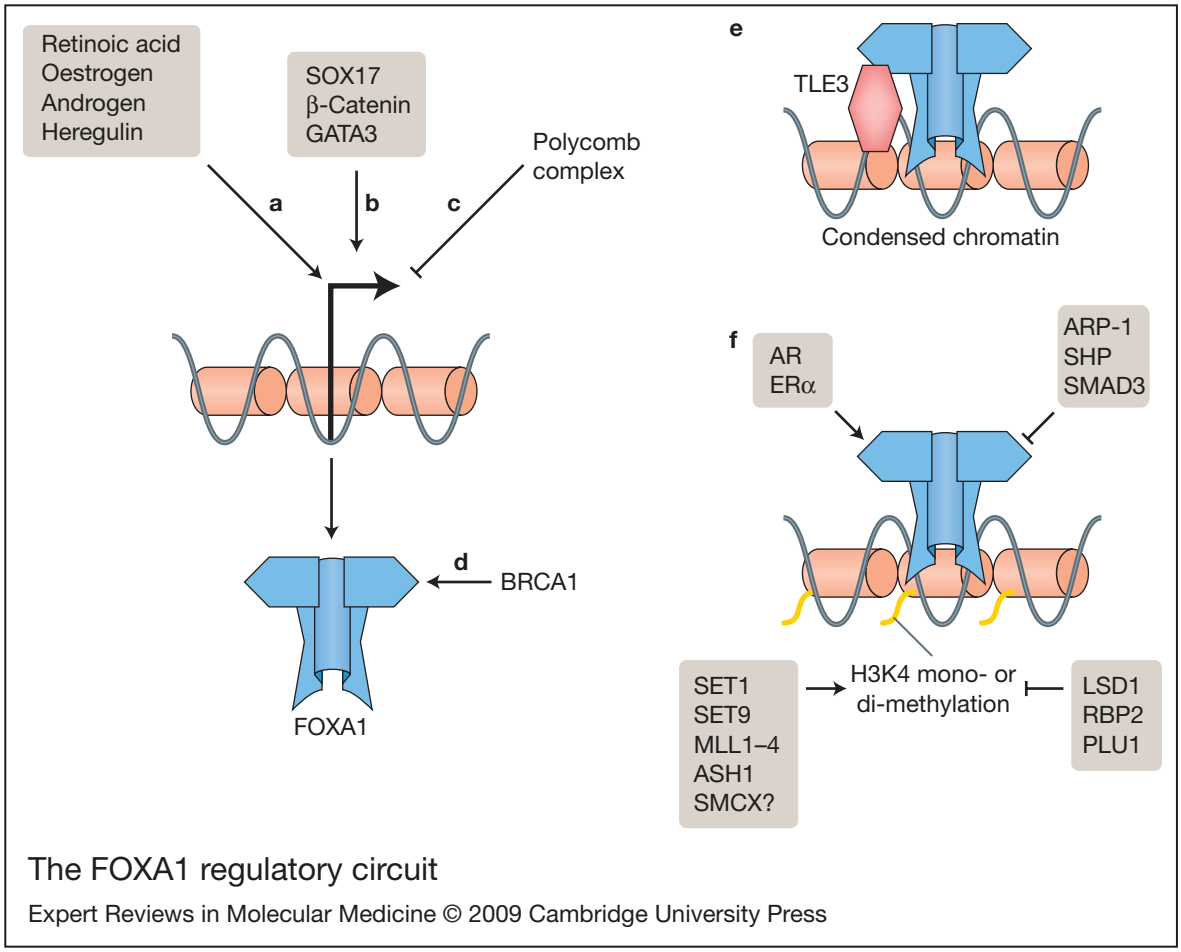


Figure 2. The FOXA1 regulatory circuit. Regulation of FOXA1 expression and activity at multiple levels is shown. *FOXA1* gene expression can be increased by (a) soluble factors such as oestrogen and (b) transcription factors such as GATA3. (c) Polycomb complex may repress expression by binding to the *FOXA1* gene. (d) BRCA1 increases the stability of FOXA1. Several factors influence the activity of FOXA1. (e) Recruitment of TLE3 by FOXA1 to chromatin represses transcription. (f) Chromatin-modifying enzymes may indirectly control FOXA1 activity by redirecting FOXA1 to specific regions of the chromatin with histone H3K4 methylation (yellow tails), and additional trancription factors may regulate the function of DNA-bound FOXA1 at such sites. Abbreviations: AR, androgen receptor; ARP-1, apolipoprotein regulatory protein 1 (also known as COUP-TFII, chicken ovalbumin upstream-transcription factor II); ASH1, absent, small or homeotic; BRCA1, breast cancer 1; LSD1, histone demethylase lysine-specific demethylase 1 (also known as BHC100); MLL1–MLL4, mixed-lineage-leukaemia proteins; PLU-1, putative DNA/chromatin-binding motif and PHD/LAP domain 1 (also known as JARIB1B); RBP2, retinoblastoma binding protein 2; SET, set-domain-containing protein; SHP, small heterodimer partner (also known as NR0B2); SMCX, X-linked mental retardation gene (also known as JARID1C); SOX17, HMG box transcription factor; TLE3, transducin-like enhancer of split 3 (also called Groucho-related protein 3, GRG3).

but not to unmethylated H3K4 (Ref. 28); and PLU-1 (also called Jumonji, AT-rich interaction domain 1B, JARIB1B) also demethylates tri- and di-methylated H3K4 (to unmethylated H3K4) but not mono-methylated H3K4 (Ref. 29) (Table 1). Overexpression of LSD1 leads to specific reduction in FOXA1 recruitment to chromatin, suggesting that the expression levels of LSD1 will impact FOXA1 function in cells (Ref. 24). Similar studies examining the effects of overexpression or reduction in the levels of other demethylases or methyltransferases on the recruitment of FOXA1 are yet to be reported. It is likely that SMCX increases FOXA1 binding as it demethylates tri-methylated H3K4 to the di- or mono-methylated form, which is preferred by FOXA1.

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Table 1. Modulators of FOXA1 function and their expression in breast cancer in relation to ERα status

Gene	Function	Expression in ERα$^+$ cancers[a]	Refs
Genes involved in *FOXA1* expression			
GATA3[b]	Induction	↑	30
RARα	Induction	↑	35
RXRα	Induction	↑	35
PPARγ	Induction	NA	34
β-Catenin	Induction	↑	38
TCF/LEF1	Induction	↑	38
Heregulin	Induction	NA	37
EZH2[c]	Repression	↓	39, 40, 41
CBX8[c]	Repression	NA	39, 40, 41
SUZ12[c]	Repression	NA	39, 40, 41
Genes that may control FOXA1 binding to target gene through H3K4 methylation[c]			
MLL1	Increased binding	↑	23
ASH1	Increased binding	↑	23
SET1	Increased binding	NA	23
SET9	Increased binding	NA	23
Genes that may control FOXA1 binding to target gene through H3K4 demethylation[c]			
LSD1[b]	Decreased binding	NA	24
PLU-1	Decreased binding	↑	29
RBP2	Decreased binding	NA	26, 27
SMCX	Increased binding	NA	28
Genes that may control FOXA1 transcriptional activity			
Androgen receptor	Increased activity	↑	19
ARP-1	Decreased activity	↑	17
SHP	Decreased activity	NA	18
SMAD3	Decreased activity	↑	21
NKX2.1	Decreased activity	NA	20, 21
TLE3	Decreased activity	↑	22
Genes that may control FOXA1 function through altered stability			
BRCA1[b]	Increased stability/activity	↑	58
FOXA1-regulated genes			
XBP1[b]	Induced	↑	4
BMP2	Induced	↓	45
MUC-4	Induced	↑	46
[$p27^{KIP1}$][b]	Induced	↑	58
SOD1[b]	Induced	NA	4
DSCAM1[b]	Induced	NA	4
PRDM15[b]	Induced	NA	4
TFF1/pS2[b]	Induced	↑	4
Cyclin D1[b]	Induced	↑	44
NDUFV3	Induced	NA	4
COL18A1	Induced	NA	4
PISD	Induced	↑	4
AP1B1	Induced	NA	4

(continued on next page)

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Table 1. Modulators of FOXA1 function and their expression in breast cancer in relation to ERα status *(continued)*

Gene	Function	Expression in ERα$^+$ cancers[a]	Refs
ATP5J	Induced	NA	4
NKX3.1	Induced	Higher level in low-grade tumours	47
BASE[b]	Repressed	NA	55

[a]Expression in ERα-positive cancers in relation to ERα-negative breast cancers. Expression levels of genes listed in breast cancer were determined using the Oncomine database (http://www.oncomine.org).
[b]Genes that were functionally analysed in breast cancer cells.
[c]The role of histone-modifying enzymes in FOXA1 function is predicted based on their enzymatic activity except for LSD1, which has been proven to inhibit FOXA1 recruitment to chromatin. Similarly, EZH2, CBX8 and SUZ12 of polycomb complex bind the *FOXA1* gene and are predicted to repress expression.
Abbreviations: ARP-1, apolipoprotein regulatory protein 1; AP1B1, adaptor-related protein complex 1, beta 1 subunit; ASH1, absent, small or homeotic; ATP5J, ATP synthase, H^+ transporting, mitochondrial FO complex, subunit F6; BASE, breast cancer and salivary gland expression gene; BMP, bone morphogenic protein; BRCA1, breast cancer 1; CBX8, chromobox homologue 8; COL18A1, collagen type XVIII alpha 1; DSCAM1, Down syndrome cell adhesion molecule 1; EZH2, enhancer of zeste homologue 2; GATA3, GATA-box-binding protein 3; LSD1, lysine-specific demthylase 1; MLL-1, mixed-lineage leukaemia 1; MUC4, mucin 4; NDUFV3, NADH dehydrogenase (ubiquinone) flavoprotein 3; NKX2.1, NK2 homeobox; NKX3.1, NK3 homeobox 1; PISD, phosphatidylserine decarboxylase; PLU-1, putative DNA/chromatin-binding motif and PHD/LAP domain 1; PPAR, peroxisome-proliferator-activated receptor; PRDM15, PR-domain-containing 15; RAR, retinoic acid receptor; RBP2, retinoblastoma binding protein 2; RXR, retinoid-X-receptor; SET1, Set-domain containing protein 1; SHP, small heterodimer partner; SMAD3, SMAD family member 3; NKX2.1, NK2 homeobox; SMCX, SMCY homologue X-linked mental retardation gene; SOD1, superoxide dismutase 1; SUZ12, suppressor of zeste homologue 2; TCF/LEF, T-cell-specific transcription factor/lymphoid enhancer binding factor; TFF1, Trefoil factor 1; TLE3, transducin-like enhancer of split 3; XBP1, X-box binding protein; NA, not available.

Nonetheless, these recent advances have begun to elucidate specific control mechanisms for the recruitment of FOXA1 to chromatin.

Regulation of *FOXA1* expression

Transcription factors that control *FOXA1* expression are just beginning to be identified (Fig. 2). In mammary epithelial cells, *FOXA1* expression is positively regulated by GATA3 (Ref. 30). GATA3 is a lineage-restricted transcription factor that is essential for the differentiation of mammary luminal progenitor cells (Refs 30, 31). Oestrogen induces *FOXA1*, possibly through oestrogen (estrogen) receptor α (ERα) (Ref. 5). Therefore, luminal epithelial cells that express ERα and GATA3 are expected to express the highest levels of FOXA1 in the mammary gland. Indeed, FOXA1, ERα and GATA3 are each expressed in a specific subpopulation of normal luminal epithelial cells (Refs 30, 32, 33) (Fig. 3), and are likely coexpressed.

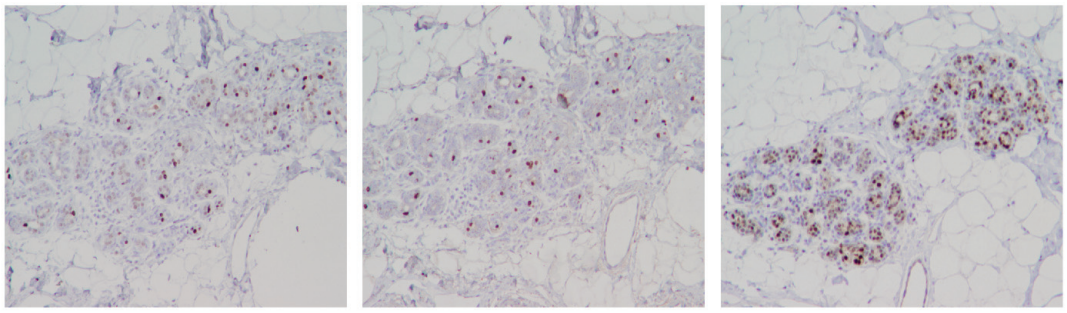
FOXA1 is induced by the nuclear receptor peroxisome proliferator activated receptor γ (PPARγ) (Ref. 34). Retinoic acid induces *FOXA1*, possibly through nuclear receptors retinoic acid receptors (RARs) and retinoid-X-receptors (RXRs) (Ref. 35). In a subset of ERα-negative breast cancer cells, AR induces the expression of *FOXA1* (Refs 36, 37). Thus, several among the 49 known nuclear receptors of the human genome control either the expression (ERα, PPARγ, RARs, RXRs and AR) or the function (SHP and ARP-1) of FOXA1 (Fig. 2).

The HMG box transcription factor SOX17 and the WNT-regulated transcription factor β-catenin positively regulate the expression of *FOXA1* (Ref. 38). In a subset of ERα-negative breast cancer cells, heregulin induces *FOXA1* expression (Ref. 37). Heregulin activates cell-surface receptors ERBB2 (v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2; also called HER2) and ERBB3; the transcription factor(s) downstream of heregulin-activated signalling involved in *FOXA1* expression is yet to be identified.

The expression of *FOXA1* in only a specific subset of luminal epithelial cells suggests 'epigenetic control' of *FOXA1* expression. Polycomb complexes are well-characterised repressor complexes involved in epigenetic negative regulation of gene expression (Ref. 39). Recent genome-wide analysis revealed specific interaction of polycomb proteins suppressor of

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FOXA1, ERα and GATA3 are expressed in luminal epithelial cells of normal breast

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Figure 3. FOXA1, ERα and GATA3 are expressed in luminal epithelial cells of normal breast. Immunohistochemistry of serial sections of normal breast reveals expression of each of these transcription factors is restricted to a subpopulation of luminal cells, as previously described (Refs 30, 32, 33).

zeste homologue 12 (SUZ12) and chromobox homologue 8 (CBX8) with the *FOXA1* gene (Refs 40, 41). As polycomb proteins show variable expression in epithelial cells, the expression levels of these polycomb proteins along with the levels of positive regulatory factors described above may demarcate the subpopulation of epithelial cells that express *FOXA1*.

FOXA1 and ERα axis in breast cancer: from obscurity to sudden prominence

Although FOXA1 was in the forefront of research into liver and prostate development and into metabolic disease for several years, its prominence in breast cancer was established only in 2005 by pioneering work of Myles Brown and colleagues (Ref. 4). While studying the binding pattern of ERα to the genome, these investigators observed specific enrichment of FOXA1-binding sites in genes that bound to ERα. These observations and subsequent studies linking GATA3 and ERα to *FOXA1* expression enabled identification of a cell-lineage-specific hormonal transcription factor network composed of ERα, FOXA1 and GATA3 (Refs 6, 30). In this network, GATA3 is upstream of FOXA1, whereas ERα functions both upstream of and parallel to FOXA1 (Fig. 2).

As discussed below, genes downstream of this network are just beginning to be identified, and use of expression signatures containing these downstream genes may help to establish the activity of this hormonal network in breast cancer. Recently, a ten-gene expression signature was reported for the diagnosis of ERα-positive invasive ductal carcinoma (Ref. 42). Subsequent meta-analysis of ERα- and GATA3-coregulated genes revealed a four-gene set that overlapped with the ten-gene signature (Ref. 43). This four-gene set includes *FOXA1* and *SLC39A6* [solute carrier family 39 (zinc transporter), member 6; also known as LIV-1] in addition to *ERα* and *GATA3*. The expression levels of SLC39A6 may serve as a marker of a functional ERα–FOXA1–GATA3 network.

Downstream targets of FOXA1

Induction of expression

The transcription factor XBP1 (X-box binding protein 1) is a direct target of ERα–FOXA1–GATA3 as it has binding sites for all three of these transcription factors (Ref. 4). Reduction of FOXA1 in MCF-7 breast cancer cells through short interfering (si) RNA caused loss of oestrogen-inducible expression of XBP1. Oestrogen-regulated expression of cyclin D1 and resveratrol-mediated ERα-dependent expression of bone morphogenic protein 2 (BMP2) require FOXA1 (Refs 44, 45). MUC-4, a transmembrane protein involved in ERBB receptor signalling, requires FOXA1 for expression (Ref. 46); however, the roles of GATA3 and ERα in MUC-4 expression are unknown. Several oestrogen-inducible genes on chromosome 21 and 22 require FOXA1 for their expression (Ref. 4).

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In prostate epithelial cells, FOXA1 increases the expression of BMP7 and NKX3.1 (Ref. 47). Whether FOXA1 similarly regulates the expression of these genes in breast epithelial and cancer cells remains to be determined. In this respect, oestrogen positively and negatively regulates NKX3.1 and BMP7 expression, respectively (Refs 48, 49). NKX3.1 expression is of particular interest because of its role in differentiation and its well-characterised tumour suppressor function (Ref. 50). Additionally, in MCF-7 breast cancer cells, NKX3.1-binding sites are enriched around ERα-binding sites, and NKX3.1 prevents ERα binding to certain regions of chromatin and modulates oestrogen-regulated expression of such genes (Ref. 51). Therefore, FOXA1-regulated expression of NKX3.1 may be critical for attenuation of oestrogen-inducible expression of select genes. NKX3.1 expression in breast cancer is mostly observed in the lobular histological type compared with ductal carcinomas (26% versus 9%) (Ref. 52). Lobular carcinomas are usually ERα-positive and better differentiated, a characteristic shared with FOXA1-positive breast cancers (Ref. 53). In this regard, FOXA1 expression is more frequent in lobular and tubular carcinoma and lower in medullary carcinoma of the breast (Ref. 54). Future studies may have to focus on elucidating the biological and prognostic relevance of the ERα–FOXA1–NKX3.1 differentiation network specific for lobular carcinomas.

Repression of expression

Although most of the research focus is on the ability of ERα and FOXA1 to induce gene expression, these factors together may also repress gene expression. For example, oestrogen-mediated repression of the *BASE* ('breast cancer and salivary gland expression') gene requires recruitment of both ERα and FOXA1 to the chromatin (Ref. 55) Therefore, the histone modifications that occur after recruitment of both factors to the *BASE* gene may be distinct from the modifications that may occur on inducible genes such as XBP1. Alternatively, FOXA1 may promote the recruitment of TLE3, which interferes with chromatin association of positively acting transcription factors (Ref. 22). Since the mechanism of oestrogen-mediated repression of gene expression is relatively poorly understood, *BASE* may serve as a model to study the ERα–FOXA1-mediated chromatin modifications in oestrogen-mediated repression of genes. Studies related to oestrogen-mediated repression of genes are as relevant as those of inducible genes because the majority of oestrogen-regulated genes are repressed by oestrogen in MCF-7 cells (Ref. 56).

In prostate epithelial cells, FOXA1 suppresses the expression of several stemness-associated genes (Ref. 47). These include the Hedgehog signalling pathway molecules SHH, GLI1 and GLI2, the Notch pathway molecule NOTCH1 and the WNT pathway molecule β-catenin. Whether these genes are similarly regulated by FOXA1 in breast epithelial and cancer cells is unknown. In breast cancer, stemness-associated gene expression is usually observed in ERα-negative breast cancers (Ref. 57). Therefore, it is likely that FOXA1 negatively regulates the expression of these genes in ERα-positive breast cancers. Additional genes negatively regulated by FOXA1 in prostate epithelial cells that may be relevant to breast cancer include fibroblast growth factor (FGF)7, FGF10 and BMP4 (Ref. 47).

A recent study described FOXA1-inducible genes that negatively regulate oestrogen-stimulated cell proliferation. For example, FOXA1 in co-operation with BRCA1 ('breast cancer 1') increases the expression of the cell cycle kinase inhibitor $p27^{KIP1}$ (CDKN1B) (Ref. 58). Oestrogen, in contrast, represses $p27^{KIP1}$ function, mostly at the post-transcriptional level (Ref. 59). Interestingly, *FOXA1* is coexpressed with *BRCA1* in primary breast cancers (Ref. 54). Thus, it appears that the ERα–FOXA1 network establishes 'one-step forward' (through cyclin D1 induction) and 'one-step backward' (through $p27^{KIP1}$ induction) modes to check cell cycle progression. These checks and balances may depend on the function of the tumour suppressor BRCA1.

Breast cancer classification and prognostic relevance of FOXA1

The traditional immunohistochemistry (IHC)-based classification scheme for breast cancer is being increasingly supplanted by molecular classification models. The 'intrinsic' molecular classification, which is based on cDNA microarray expression data, classifies breast cancer into five groups: luminal A, luminal B, HER2-positive, basal and normal subtypes (Ref. 60). Expression of ERα is seen in the luminal groups but not in other subtypes. These molecular classification models will dramatically impact clinical practice as

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individualised treatments are likely to become standard care in the near future. However, surrogate histopathological markers that mimic the molecular classification are being sought for clinical use (Ref. 61). The most commonly used definition categorises tumours that express both ERα and progesterone receptor (PR) as luminal A and the other ERα-positive tumours including those that express HER2 as luminal B (Ref. 62). FOXA1 also appears to be a marker that can effectively bridge the two types of classification tools.

When we analysed FOXA1 protein expression in breast cancers by IHC in relation to intrinsic subtypes, FOXA1^{high} (score greater than 3 by IHC) was associated with ERα positivity, GATA3 positivity and luminal A subtype (Ref. 32). Most significantly, improved event-free survival was seen in these patients compared with patients in the FOXA1^{low} group, and this difference was significant even at 20 years. Additionally, FOXA1 expression was found to be a better predictor of survival than PR. When the analysis was stratified based on lymph-node positivity, FOXA1-positive patients in both node-positive and unknown nodal status groups had a better prognosis than FOXA1-negative patients. It is important to note that a specific subpopulation of normal luminal epithelial cells express FOXA1 at levels similar to those in FOXA1^{high} group of patients. Therefore, *FOXA1* expression in breast cancers may indicate cell type origin and differentiation status of breast cancer rather than cancer-specific overexpression.

Analysis of FOXA1 expression in another tissue microarray of ~250 patients treated with standard adjuvant therapy also demonstrated the prognostic value of FOXA1 (Ref. 63). A third study analysed the expression of FOXA1 in a series of ~850 patients (Ref. 54). This study differed significantly from the previous two studies with respect to methodologies; different reagents were used for IHC (mouse monoclonal rather than goat polyclonal antibody in the other two studies) as well as a different cut-off point for positivity (H-score of 10 rather than 30). Despite these differences, the study demonstrated almost identical results in terms of association with luminal A subtype. FOXA1 expression was also associated with disease-free survival and overall survival; however, this association did not retain significance in multivariate analysis. One of the findings of this study is intriguing as it relates to hormonal therapy. In the group of patients that did not receive hormonal therapy, FOXA1 expression was found to be associated with favourable breast-cancer-specific survival. However, no significant differences in breast-cancer-specific survival or disease-free interval were observed between FOXA1^{high} and FOXA1^{low} patients treated with the hormonal therapy tamoxifen. This suggests that response to tamoxifen therapy depends more on luminal type A or B phenotype rather than FOXA1 expression alone.

Expression of FOXA1 in ERα-negative tumours has been correlated with the expression of AR (Ref. 36). FOXA1 expression in these cells is suggested to be due to crosstalk between AR and ERBB2 signalling and to represent part of an AR-mediated hormone-responsive programme in ERα-negative/PR-negative breast cancers (Ref. 37). Although three IHC-based studies and several gene expression analyses showed an association of FOXA1 with ERα-positive/luminal type A breast cancer, a cell-line-based study found an association between FOXA1 mRNA expression and ERBB2/HER2-positive phenotype (Ref. 64).

FOXA1 expression and current clinical practice

Oncotype DX is one of the major commercially available, clinically applicable diagnostic tools that has emerged from gene expression analysis (Ref. 65). This diagnostic tool is being used to decide adjuvant therapy for patients with ERα-positive and node-negative breast cancers. This reverse transcription–polymerase chain reaction (RT-PCR) assay examines the expression of 16 genes (*Ki67*, *STK15*, survivin, *CCNB1*, *MyBL2*, *MMP11*, *CTSL2*, *GRB7*, *HER2/ERBB2*, *GSTM1*, *CD68*, *BAG1*, *ERα*, *PR*, *BCL2* and *SCUBE2*). The expression pattern of each of these genes is tabulated using an equation, and a recurrence score (RS) is assigned to each case. Among these genes, higher expression levels of ER, PGR, BCL2, SCUBE2, GSTM1 and BAG1 reduce RS (negative values), whereas higher expression levels of remaining genes increase RS. ERα-positive patients with higher RS benefit from chemotherapy in addition to hormonal therapy (Ref. 66).

Chromatin immunoprecipitation (ChIP)-coupled microarray (ChIP-on-chip) studies in MCF-7 breast cancer cells revealed oestrogen-dependent binding of ERα to seven of the

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above the 16 genes (survivin, *MyBL2*, *HER2/ERBB2*, *BAG1*, *ER*, *PR* and *SCUBE2*) (Ref. 67). Currently, the influence of oestrogen on the expression of only five of the 16 genes is known: oestrogen increases *PR*, *CCNB1* and *BCL2* expression but decreases *HER2/ERBB2* expression, and derepresses survivin from p53-mediated repression (Ref. 68). Additionally, GRB7 confers oestrogen independence to breast cancer cells (Ref. 69). The requirement of FOXA1 in ERα binding and oestrogen-regulated expression of the above genes is unclear at present. We propose that FOXA1 and its downstream targets such as NKX3.1 influence RS by modulating ERα-mediated induction or repression of some of these genes.

MapQuant Dx™ (previously called genomic grade index) is a newly commercialised diagnostic tool that combines the expression levels of 97 genes to help discriminate between histological grades 1 to 3 (Ref. 70). It can be used to decide whether ERα-positive and node-negative patients should receive chemotherapy (Ref. 71). Among these genes, 42 are regulated by oestrogen in MCF-7 breast cancer cells (Ref. 67). Interestingly, *FOXA1* is not one of the 97 genes. Elucidating the role of FOXA1 in oestrogen-dependent and oestrogen-independent expression of these genes may reveal the mechanism of histological-grade-dependent increase in the expression of some of these genes in ERα-positive breast cancers. If indeed reduction in FOXA1 expression in an experimental setting leads to elevated expression of the above genes, one could replace the expensive MapQuant Dx™ with simple IHC for FOXA1 to determine additional benefits of chemotherapy for ERα-positive breast cancer.

Do modulators of FOXA1 expression and/or activity add prognostic value to FOXA1 in breast cancer?

Cell-culture-based studies have clearly shown a role for multiple proteins in regulating the function of FOXA1. The fact that some patients in the FOXA1^{high} group still succumb to disease raises the possibility that certain functions of FOXA1 are impaired in these patients. Also, the expression levels of FOXA1 in normal breast epithelial cells and FOXA1^{high} cancer cells are similar. This observation suggests that FOXA1 function but not the expression is impaired in cancer cells compared with normal cells. There are plenty of unanswered questions regarding cancers with an ERα-positive and FOXA1^{low} phenotype. Is this phenotype due to a progressive loss of FOXA1 expression in cancer cells due to elevated expression of polycomb proteins? Alternatively, do these cancers originate from ERα-positive cells that naturally express low levels of FOXA1? This can be partially addressed through data mining of already available breast cancer gene expression studies looking specifically at the expression of genes that regulate FOXA1 function. Several genes that positively regulate FOXA1 function are overexpressed in ERα-positive breast cancers compared with ERα-negative breast cancers (Table 1). For example, MLL, which mediates H3K4 methylation, is overexpressed in node-negative and ERα-positive breast cancers compared with ERα-negative breast cancers. Similarly, ASH1, which functions similarly to MLL, is overexpressed in ERα-positive breast cancers. PLU-1, which demethylates tri- and di-methylated H3K4, is overexpressed in ERα-positive breast cancers. PLU-1 functions as a transcription repressor in breast cancer cells by repressing the expression of BRCA1 and is required for breast cancer proliferation (Ref. 29). BRCA1 has been shown to interact with FOXA1 and increase its stability (Ref. 58). Thus, in ERα-positive breast cancers that overexpress PLU-1, FOXA1 expression and/or activity may be attenuated. RAR, a positive regulator of FOXA1 function, and ARP-1, a negative regulator of FOXA1 function, are overexpressed in ERα-positive breast cancers. Similarly, TLE3, which represses FOXA1 target gene expression (Ref. 22), is overexpressed in ERα-positive breast cancers. Therefore, the ability of FOXA1 to direct ERα to specific genes as well as to regulate the expression of differentiation- or proliferation-associated genes may depend on the expression pattern of genes that influence FOXA1 activity.

Is FOXA1 a target for differentiation therapy?

All four studies that compared FOXA1 expression in primary breast cancer have established FOXA1 as a good prognostic marker for ERα-positive breast cancers (Refs 32, 54, 63, 72). In vitro studies have clearly shown that FOXA1 and ERα are functionally linked (Refs 4, 5). The functional link between these transcription factors may be associated with a higher level of differentiation

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and lower histological grade. If that is the case, can differentiation of ERα-positive breast cancers be enhanced by therapeutic increase in FOXA1 expression? Ligands for nuclear receptors have been reported to induce FOXA1. One is the ligand for PPARγ (Ref. 58), which is already in clinical use as antidiabetic therapy. The second is retinoic acid or its synthetic derivatives (Ref. 35). Retinoic acids have previously been shown to induce growth arrest or apoptosis of ERα-positive breast cancer cells (Ref. 73). Although synthetic retinoids have been tested in clinical trials (Ref. 74), targeting these retinoids to only ERα-positive breast cancers with low FOXA1 expression may enhance their therapeutic value. The acute-phase response, inflammation and polycomb repressor complexes are likely to decrease FOXA1 expression (Refs 40, 41, 75). Therefore, drugs with anti-inflammatory properties or that reduce polycomb complex may increase FOXA1 expression and induce differentiation of ERα-positive breast cancers.

Future directions

Significant progress has been made in understanding the role of FOXA1 in development and differentiation. Its function in cancer is mostly studied in the context of prostate cancer. Some of the knowledge gained from these studies is beginning to be applied to breast cancer. However, significant gaps exist in our knowledge of the normal luminal cell type that expresses FOXA1 and of the relationship between FOXA1, ERα and GATA3 expression. There is no evidence to indicate a cancer-specific increase in FOXA1 expression due to amplification or mutations in breast cancer. However, FOXA1 expression may decrease as the cancer progresses due to an increase in polycomb complex activity. Therefore, future efforts need to focus on testing whether a lack of FOXA1 expression in cancer is indicative of cell type origin or a progressive increase in the activity of polycomb complexes leading to the epigenetic silencing of FOXA1 expression. Cancers with active silencing of FOXA1 expression may benefit from epigenetic/differentiation therapies.

Only a subset of normal luminal epithelial cells express ERα, FOXA1 and GATA3 (Fig. 3). Methods that can simultaneously analyse the expression of ERα, FOXA1 and GATA3 in a single cell in a laboratory and/or clinical setting may help to dissect the luminal-cell-type-specific oestrogen response and the susceptibility of different cell types to cancer, and to assess response to hormonal therapy.

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Further reading, resources and contacts

Publications

Sotiriou, C. and Piccart, M.J. (2007) Taking gene expression profiling to the clinic; when will molecular signatures become relevant to patient care? Nature Reviews Cancer 7, 545-553
This is a useful review that discusses limitations and promises of gene expression studies for individualised breast cancer therapies.

Andre, F. and Pusztai, L. (2006) Molecular classification of breast cancer; implications for selection of adjuvant chemotherapy. Nature Clinical Practice Oncology 3, 621-632
This review discusses predictors of prognosis and response to chemotherapy in breast cancer.

Website

The Cancer Trials Support Unit (CTSU) supports a national network of physicians to participate in National Cancer Institute (NCI)-sponsored Phase III clinical trials:

http://www.ctsu.org

Features associated with this article

Figures

Figure 1. FOXA1 functional domains.
Figure 2. The FOXA1 regulatory circuit.
Figure 3. FOXA1, ERα and GATA3 are expressed in luminal epithelial cells of normal breast.

Table

Table 1. Modulators of FOXA1 function and their expression in breast cancer in relation to ERα status.

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