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Review

About *GATA3*, *HNF3A*, and *XBP1*, three genes co-expressed with the oestrogen receptor-α gene (*ESR1*) in breast cancer

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Abstract

In breast tumours and breast cancer cell (BCC) lines, microarray analyses have revealed that a series of genes are expressed in close association with the oestrogen receptor-α (ER-α) gene, *ESR1*. Three of them, *GATA3*, *HNF3A* (also known as *FOXA1*), and *XBP1* encode transcription factors. Here, we present these factors and we discuss their potential involvement in the ER-α-mediated actions in BCC. We notably show the relations that exist, or that might exist, between these factors and the oestrogen-inducible trefoil factor TFF1.

Keywords: Breast cancer; Oestrogen receptor-α; GATA-3; HNF-3α; XBP-1; TFF1

1. Introduction

The main mediator of anti-oestrogens action, the oestrogen receptor-α (ER-α, gene *ESR1*), plays a key role in the biology and treatment of breast cancer (Osborne et al., 2001; Leclercq et al., 2002). Global gene expression analyses have revealed that it is a major discriminator in breast cancer and breast cancer cell (BCC) lines classification. Numerous studies, notably based on microarray use, have shown that the expression of *GATA3*, *HNF3A* (also known as *FOXA1*), and *XBP1* is strongly and positively correlated to that of *ESR1* (Hoch et al., 1999; Perou et al., 2000; Bertucci et al., 2000; Sorlie et al., 2001, 2003; West et al., 2001; Gruvberger et al., 2001; Ross and Perou, 2001; van't Veer et al., 2002; Sotiriou et al., 2003; reviewed in Lacroix and Leclercq, 2004). These genes encode transcription factors, the role of which in regulating BCC activities remains largely unknown. In an attempt to solve this question, we reviewed the literature concerning the biological function of these proteins. On the basis of these data, we suggest their possible involvement in the ER-α-mediated responses of BCC.

2. Characteristics and functions of factors encoded by *GATA3*, *HNF3A*, and *XBP1*

2.1. GATA-binding protein 3

GATA-3 is member of a family of six (GATA-1 to -6) transcription factors containing two zinc fingers. The C-terminal finger is capable of tight, specific binding to the (A/T)GATA(A/G) consensus DNA sequence. Differences in the N-terminal DNA binding domain are likely to provide a mechanism for more selective transcriptional control of target genes by the various GATA proteins (Takemoto et al., 2002). Whereas GATA-1, -2, and -3 expression has been predominantly observed in haematopoietic cells, GATA-4, -5, and -6 are observed mainly in the cardiovascular system and in endoderm-derived tissues including liver, lung, pancreas, and gut. GATA-binding sequences are often found interspersed among other common DNA elements suggesting that GATA factors might essentially function in co-operation with other DNA binding proteins. In general, GATA proteins have been shown to play critical roles in development, including cell-fate specification, regulation of differentiation, and control of cell proliferation and movement.

Most of our knowledge on GATA-3 action results from the key role of this factor in the development of T-cell lineage

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and the differentiation of naive CD4+ T-cells into Th2 as opposed to Th1 effectors cells. In Th2 cells, factors that increase cAMP levels may activate GATA-3, notably through p38 kinase-mediated phosphorylation. Binding of GATA-3 in the regulatory regions of various genes, including IL-4, IL-5, and IL-13 alters the chromatin structure, increasing accessibility to other transcription factors (Chen et al., 2000; Klein-Hessling et al., 2003). Of interest, the presence of ER-α has been demonstrated in T-cells (see, for instance, Rider and Abdou, 2001).

GATA-3 is present in prostate and breast, two steroid hormone-dependent tissues. In the upstream promoter region of two prostate-specific genes, *KLK2* and *KLK3* (formerly *PSA*, encoding prostate specific antigen), an androgen-responsive element (ARE) is flanked by multiple GATA-binding sites (six in the far-upstream enhancer of *KLK3*). Data from promoter reporter experiments support a role for GATA-3 in the androgen regulation of *KLK3* (Yu et al., 1999; Perez-Stable et al., 2000). The strong correlation between ER-α and GATA-3 expression in BCC [first described by (Hoch et al., 1999)] leads us to speculate that GATA-3 might similarly co-operate with this steroid receptor to regulate breast-specific hormone-responsive genes.

The *HSD17B1* gene encodes the 17beta-hydroxysteroid dehydrogenase type I involved in the redox inter-conversion of the weak oestrogen, oestrone, to the potent oestrogen, oestradiol (E_2). *HSD17B1* is expressed in breast luminal-epithelial cells. In choriocarcinoma cells, GATA-3 was demonstrated to bind to a *HSD17B1* silencer region, and mutations introduced into the GATA-binding site increased transcriptional activity to the level seen in gene constructs not containing the silencer element. Thus, GATA-3 might operate as a negative control element for *HSD17B1* transcription (Piao et al., 1997).

TFF1 (formerly pS2) is a trefoil factor encoded by the *TFF1* gene. In BCC lines and tumours, TFF1 expression is highly correlated to that of ER-α (see notably, Gillesby and Zacharewski, 1999). In a variety of tumour cell lines of gastric, intestinal, and pancreatic origin, a member of the GATA family, GATA-6, has been shown to activate *TFF1* transcription. Located in the 5′-flanking region of this gene are several consensus sequences for GATA proteins, in a direct or reverse orientation (Al-Azzeh et al., 2000). One of them is found immediately downstream the CAAT box (see Fig. 1). Whether *TFF1* could be induced by GATA-3 in BCC is, however, unknown as yet.

2.2. Hepatocyte nuclear factor-3α

HNF-3α, also known as forkhead box A1, is member of a family of three transcription factors (the two others being HNF-3β/forkhead box A2 and HNF-3γ/forkhead box A3) containing a forkhead or winged helix as the DNA-binding domain. HNF-3 proteins were discovered by their ability to bind to TGTTTG(C/T) or TGTTTGCT sequences in the promoter or enhancer regions of genes encoding alpha1-antitrypsin (*SERPINA1*) and transthyretin (*TTR*) (Costa et al., 1989). Subsequently, HNF-3-binding sites have been discovered in dozens of genes that are expressed in the liver, pancreas, intestine, and lung, as well as

Fig. 1. Nucleotide sequence of the *TFF1* proximal promoter. The various binding sites described in the text are indicated. Underlined sequences are regions associated with nucleosomes NucE and NucT, according to Métivier et al. (2003) (single underlined) and Sewack and Hansen (1997) (double underlined).

during embryogenesis (Vallet et al., 1995; Cereghini, 1996; Tomaru et al., 2003). Genetic analysis in mice has shown that HNF-3α is required in the pancreas for full activation of glucagon (Kaestner, 2000) thus contributing to glycogen hydrolysis and glucose production. A key role of the factor in the regulation of glucose homeostasis is also suggested by the presence of HNF-3α sequences in genes encoding glycogen synthase and glycogen phosphorylase (Tomaru et al., 2003).

In addition to directly allowing transcription of target genes via its trans-activation domain, HNF-3α appears to promote gene expression by altering chromatin structure. Its winged helix domain appears strikingly similar to that of linker histones H1 and H5 (Clark et al., 1993). The function of the linker histones is to restrict the DNA on the nucleosome surface, leading to inactivation of gene transcription. HNF-3α can bind to specific DNA sequences on the nucleosome core and displace the linker histones. As it lacks the basic amino acids present in linker histones required to mediate compaction of nucleosomal DNA (Cirillo et al., 1998), the net result of its binding may be to de-compact chromatin and to facilitate binding of other transcription factors to gene promoters (Kaestner, 2000). Demonstration that HNF-3α-directed structural changes functionally mediate de-repression of transcription on a chromatin template has been shown with the albumin gene (McPherson et al., 1993; Shim et al., 1998).

HNF-3α is expressed in various epithelial tissues: respiratory epithelium, intestinal and colonic epithelium, epithelium of the kidney, urinary bladder, penile urethra, and the prostate gland. This suggests that it might favour the action of tissue and organ-specific factors. In adult rats, HNF-3α level was sustained by exogenous testosterone after castration (Kopachik et al., 1998) supporting a narrowed relationship between the factor and the steroid hormone. Indeed, HNF-3α is essential for androgen receptor (AR)-mediated prostatic gene *KLK3* regulation. In the *KLK3* core enhancer region, there are several ARE and two HNF-3-binding sequences. Mutations that disrupt these HNF-3 motifs significantly reduced the maximal androgen induction of *KLK3*. Over-expression of a mutant HNF-3α deleted in the C-terminal region inhibited the androgen-induced *KLK3* promoter activity in LNCaP cells. Chromatin immune-precipitation revealed that, in vivo, the occupancy of HNF-3α on *KLK3* enhancer could occur in an androgen-depleted condition before the recruitment of ligand-bound AR. A physical interaction of HNF-3α and AR was detected, which was mediated directly through the DNA binding domain/hinge region of AR and the winged helix domain of HNF-3α (Gao et al., 2003).

HNF-3α and ER-α co-operatively activate transcription of the liver-specific vitellogenin B1 gene when present during chromatin assembly indicating either that they somehow interact physically or that HNF-3α helps the recruitment of ER-α on a loosened chromatin environment (Robyr et al., 2000).

CYP3A4 is highly expressed in human liver. Its protein product, cytochrome P450 3A4 has the ability to metabolise a large number of clinically used drugs and activate xenobiotics to reactive metabolites. In breast tumours, it may metabolise E_2 (Kristensen and Borresen-Dale, 2000). In the *CYP3A4* promoter, an HNF-3-binding site (−187 to −194) is close to an oestrogen-responsive element (ERE) (−202 to −212) suggesting that HNF-3α may participate in the oestrogen regulation of the gene (Gibson et al., 2002).

In pancreatic and gastric cell lines, HNF-3α was shown to activate a *TFF1* reporter gene by interacting with a sequence located close to the TATA box (Fig. 1) (Beck et al., 1999). Another well-known inducer of *TFF1* transcription is ER-α (see, for instance, Kim et al., 2000), which interacts with an imperfect ERE (Nunez et al., 1989). It seems that two other sequences located near the ERE are needed for full ER-α activity: an AP-1 site (Barkhem et al., 2002) and an oestrogen receptor-related-α response element (ERRE; Lu et al., 2001) (see Fig. 1).

The human *TFF1* proximal promoter contains two phased nucleosomes, termed NucE and NucT, as they include at their edge either the ERE or the TATA box, respectively (Sewack and Hansen, 1997). It has been shown later that these nucleosomes are not immobile, as initially believed, but that they cyclically fluctuate around their preferred positions (Métivier et al., 2003). As shown in Fig. 1, NucE also covers the AP-1 and ERRE sequences. On the other hand, the *TFF1* promoter region associated with NucT not only include the TATA box but also the CAAT box, the HNF-3-binding sequence, and the four putative GATA-binding sequences identified by Al-Azzeh et al. (2000). This suggests that not only HNF-3α but also GATA-3 could play some role in *TFF1* transcription by allowing an open chromatin configuration in the vicinity of the TATA box.

2.3. X-box-binding protein 1

XBP-1 is a basic leucine zipper (bZIP)-containing transcription factor capable of specific binding to the DNA consensus sequence CCAAT(N9)CCACG, also named endoplasmic reticulum stress response element I (ERSE-I). XBP-1 is intimately associated to the so-called “unfolded protein response” (UPR).

The endoplasmic reticulum (EnR) is the entrance site for proteins destined to reside in the secretory pathway or the extra-cellular environment. It is also the site of biosynthesis for steroids and many lipids. Thus, the EnR must manage the correct folding and the efficient trafficking of a considerable number of molecules (Rutkowski and Kaufman, 2004). UPR consists in various mechanisms allowing the EnR to prevent the accumulation of unfolded or aggregated proteins and correct or discard misfolded proteins. UPR involves up-regulation of chaperones (including glucose-regulated proteins) production, attenuation of general protein translation, and degradation of irrecoverable

misfolded proteins by shipment to the proteasome. Glucose plays a key role in UPR as this latter may be triggered by glucose deprivation. However, this sugar not only provides the metabolic energy needed by cells but also participates directly in glycoprotein folding as a component of oligosaccharide structures. The recognition and modification of oligosaccharide structures in the lumen of the EnR is intimately coupled to polypeptide folding. Problems arising during this process cause EnR stress and are detected by molecular EnR sensors, one of which is IRE1 (inositol-requiring 1). IRE1 is a type 1 transmembrane serine/threonine protein kinase that also has site-specific endoribonuclease (RNAse) activity. The presence of unfolded proteins in the EnR lumen promotes dimerization and trans-autophosphorylation, rendering IRE1 active as an RNase, and allowing it to remove a 26-nucleotide intron in *XBP1* RNA and generate a translational frame-shift. This results in the replacement of the "unspliced" 267-aminoacids long XBP1 (XBP-1u) by a "spliced" protein (XBP-1s), which has 371 amino acids and a novel carboxyl-terminus that acts as a potent transcriptional activator, notably of chaperone genes (Kaufman, 2002).

Proteasome inhibition may induce cell death in proliferating cells suggesting that proteasome function is required for tumour cell survival (Dou et al., 2003). It has been recently shown that proteasome inhibitors such as MG-132 and PS-341 disrupt the UPR and cause apoptosis in myeloma cells by targeting the XBP-1 pathway (Lee et al., 2003). This underlines the importance of XBP-1 as a mediator of UPR.

XBP-1 is ubiquitously expressed in adult tissue. However, its mRNA is found at higher levels in ER-α-positive than in -negative breast tumours, although the forms (spliced or unspliced) of the resulting XBP-1 proteins are unknown. The gene is up-regulated as early as 2 h following E_2 treatment and down-regulated by the anti-oestrogen ICI 182,780 (Bouras et al., 2002; Wang et al., 2003; Cunliffe et al., 2003). It is of interest that *XBP1* mRNA must be induced to a significant level to produce XBP-1s at levels sufficient for detection and trans-activation (Yoshida et al., 2001). Induction of *XBP1* mRNA by activated ER-α could thus favour this "spliced" form.

It has been shown that XBP-1s and XBP-1u enhanced ER-α-dependent transcriptional activity in a ligand-independent manner. XBP-1s had stronger activity than XBP-1u. Both forms bound to the ER-α in vivo and in vivo in a ligand-independent fashion. Both a pure (ICI 182,780) and a partial (4-hydroxytamoxifen, 4-OHT) anti-oestrogen completely blocked the effects of XBP-1u on ER-α transcriptional activity in the presence or absence of E_2, whereas both ICI 182,780 and to a lesser extent, 4-OHT, reduced but did not abolish the ability of XBP-1s to trans-activate ER-α. The steroid receptor co-activator SRC-1/NCoA1 synergized with XBP-1s or XBP-1u to potentiate ER-α activity. It is possible that ER-α recruits XBP-1 to the ERE-containing promoter to stimulate gene transcription (Ding et al., 2003).

While GATA- and HNF-3-binding sequences have been found in the proximal promoter of the *TFF1* gene, we identified no XBP-1-binding sequence in this promoter. This suggests that *TFF1* is not directly regulated in UPR.

3. Differences and similarities in mechanisms underlying *ESR1, GATA3, HNF3A,* and *XBP1* expression: a few words

Despite the close correlation existing between *ESR1*, *GATA3*, *HNF3A*, and *XBP1* expression in breast cancer, none of the factors encoded by the three latter genes has been shown to date to play a role in *ESR1* regulation. Interestingly, a microarray-mediated study has shown that *GATA3*, *HNF3A*, and *XBP1* expression is not correlated to that of *ESR1* in ovarian tumours. Indeed, these three genes appear more highly expressed in breast cancer than in ovarian carcinomas (Schaner et al., 2003). It is well known that *ESR1* mRNA may be transcribed from at least six different promoters exhibiting tissue specificity (Flouriot et al., 1998). While promoter A is abundantly used in BCC/breast cancer, promoters C and F are preferentially used in ovarian carcinomas. Whether regulatory factors involved in *GATA3*, *HNF3A*, and *XBP1*, expression could also specifically interact with sequences in the A promoter remains to be established. A major factor involved in *XBP1* expression is ATF6. Its involvement in *ESR1*, *GATA3* or *HNF3A* expression has not been demonstrated till date. *HNF3A* is a primary target for retinoic acid action and its promoter contains a retinoic acid response element (RARE) (Jacob et al., 1999). Agonists of the retinoid-X-receptor (RXR) may enhance the level of *GATA3* mRNA and in vivo Th2 cell development from CD4+ T-cells (Stephensen et al., 2002). The α subtypes of retinoic acid receptor (RAR) and RXR are frequently found in breast carcinoma and the expression of both is correlated to that of ER-α (Suzuki et al., 2001). Thus, there seems to be a link between *ESR1*, *GATA3*, and *HFN3A* expression in breast cancer and the action of retinoids, which are known to be differentiating agents in BCC. No effect of retinoids on *XBP1* expression has been shown as yet. In summary, mechanisms underlying *ESR1*, *GATA3*, *HNF3A*, and *XBP1* expression in BCC appear at least partly different.

4. Potential involvement of GATA-3, HNF-3α, and XBP-1 in ER-α-mediated actions in BCC

Biological properties reported over here suggest that all three factors described can or could be actors in steroid receptor-mediated transcription of target genes. An involvement of GATA-3 and HNF-3α in the androgen regulation of prostate-specific genes has been documented, and data available strongly suggest that like XBP-1, they could modulate the ER-α-mediated gene regulation in BCC.

The induction of cell proliferation is a major effect mediated by ER-α in BCC. This process needs energy to occur and supposes a massive synthesis of proteins. At least two of the described factors, HNF-3α and XBP-1, have an action related to glucose homeostasis. XBP-1 splicing and action on specific promoters are dependent of the level of glucose. HNF-3α is a key actor in controlling glucose availability and it is speculated that it could specifically favour the regulation by ER-α of metabolism-associated genes in BCC. On the other hand, an intensive protein synthesis may potentially lead to EnR stress and the triggering of UPR. The co-expression of mRNAs specific for ER-α and an essential UPR-associated factor (XBP-1) appears, thus, logical. The fact that ER-α trans-activation may be facilitated by XBP-1 suggests that the activity of the receptor could be closely dependent of the ability of cells to manage their EnR stress.

One way to control ER-α activity is to modulate the availability of its ligand. A role for HNF-3α and GATA-3 in this process is suggested by the presence of their specific binding sequences in the promoter of genes involved in both the synthesis (*HSD17B1*) and the degradation (*CYP3A4*) of E_2.

The expression of several genes is closely correlated to that of *ESR1*, *GATA3*, *HNF3A*, and *XBP1*. Two of them are *TFF3* and *LIV-1*. The first encodes a secreted trefoil factor related to *TFF1* and frequently expressed with this latter, notably in breast tissues (Poulsom et al., 1997). The membrane protein encoded by the second appears to transport zinc into cells (Taylor et al., 2003). Both genes are induced by oestrogens. The structure of their respective promoters remains, however, poorly characterized, which deserves further studies on their possible regulation by ER-α, GATA-3, HNF-3α, and XBP-1.

One plausible candidate for gene regulation through the likely complex interplay of ER-α, GATA-3, and HNF-3α is *TFF1*. Its expression is correlated to that of ER-α (see, for instance, Gillesby and Zacharewski, 1998). TFF1 has been shown to directly bind to mucins (Tomasetto et al., 2000). It is often remarkably increased at sites of injury, inflammation, and tumours (pancreas, stomach, breast) (Luqmani et al., 1992). Like other trefoil factors, it is able to enhance epithelial cell motility and spreading, and may accelerate mucosal recovery/restitution after injury of the gut (Wright, 1993; Dignass et al., 1994; Playford et al., 1995). TFF1 participates in gastrointestinal cell differentiation by delaying G_1–S phase transition and reducing apoptosis. TFF1 diminishes by 50% the S phase cell entry, leading to increased expression of cyclin-dependent kinases inhibitors (Bossenmeyer-Pourié et al., 2002). TFF1 has been shown to significantly stimulate MCF-7 and MDA-MB-231 BCC movement. In the ER-α-expressing MCF-7 cells, little cell movement was observed in the absence of oestrogens. Migration was stimulated by the addition of oestrogen or exogenous TFF1. The concentrations at which TFF1 stimulates BCC migration were similar to those detected in medium conditioned by oestrogen-treated BCC in culture. This suggests that TFF1 acts as an oestrogen-regulated autocrine mitogen in BCC. As TFF1 may be viewed as a global player in epithelial restitution, its gene is expected to be regulated in a complex way in conditions of cell proliferation.

DNase I footprinting experiments performed on the *TFF1* promoter have identified, close to the translation initiation site, three regions protected in MCF-7 cells in absence as well as in presence of 10 nM E_2 (see Fig. 7 in Kim et al., 2000). In fact, these protected regions (not shown) appear to correspond to, or to include, the TATA box, the HNF-3-binding sequence, and the proximal putative GATA-binding sequence. This indicates that proteins are permanently bound to these sites. We suggest that in ER-α-expressing BCC, GATA-3, and HNF-3α could be two of these proteins.

We propose that in MCF-7 BCC, binding of GATA-3 and HNF-3α to their corresponding promoter sites could open the chromatin structure around NucT and allow a permanent low-level of *TFF1* expression. The binding of activated ER-α to its own sequence will open the chromatin structure around NucE and lead to the recruitment of a complex molecular machinery resulting in a considerable increase in *TFF1* transcription. Whether GATA-3 and HNF-3α, or their associated proteins, could interact with proteins composing the highly complicated molecular architecture recruited by the ER-α (see notably, Métivier et al., 2003) remains a purely speculative issue.

On the other hand, a link between TFF1 and XBP-1 may be inferred from data indicating that TFF1 could prevent UPR. *TFF1*-null mice develop antropyloric tumours (Lefebvre et al., 1996). Differential expression analyses of these *TFF1*-null antropyloric tumours revealed the common and permanent (up to 1 year) up-regulation of a series of genes associated to unfolded protein response. Moreover, consistent with UPR, ultra-structural analyses showed that tumour rough EnR was enlarged and contained dense material supporting the hypothesis that TFF1 deficiency leads to the accumulation of misfolded proteins in the organelle (Torres et al., 2002). As XBP-1 is a key mediator of UPR, it is likely (although, not demonstrated to date) that TFF1 could regulate the amount of its mRNA.

In conclusion, there are data suggesting that GATA-3, HNF-3α, and XBP-1 play an important role in accompanying and controlling ER-α-mediated effects in BCC. This deserves further studies on the exact function of these factors in cancerous but also in normal breast epithelium.

Uncited reference

Giordano et al. (2001).

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