The ATF/CREB Family of Transcription Factors in Breast Cancer

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1. Introduction

Transcription factors are proteins that bind DNA and either promote or block gene transcription. The activating transcription factor/cyclic AMP response element binding (ATF/CREB) family of transcription factors are involved in various cellular processes, including cell stress responses, cell survival, and cell growth. In this chapter, we will first give an overview of the transcriptional regulation of oncogenesis, followed by a brief summary of the roles of ATF/CREB family members in breast cancer. After this, we will describe the structure of ATF/CREB family members and then go into detail concerning each ATF/CREB family member that has a function relevant to breast cancer. Finally, we will end the chapter with some forward-looking remarks on ATF/CREB-based breast cancer therapeutics.

2. Transcriptional regulation in breast cancer

Transcription factors play an important role in breast cancer tumorigenesis and progression. For example, ETS1, ELF3, PDEF, PEA3, HIF-1, and MYC are all transcription factors that are overexpressed in breast cancer (Kurpios and others 2003). Overexpression of MYC in MCF7 human non-metastatic breast cancer cells causes those cells to display a metastatic-like phenotype (de Launoit and others 2000). The transcriptional targets of PEA3 include MMP1, MMP3, MMP9, vimentin, and ICAM-1, genes that are involved in breast cancer cell invasion and migration (de Launoit and others 2000). Other transcription factors involved in breast cancer include snail, which blocks E-cadherin transcription (Cano and others 2000); CBP/p300, a transcriptional co-activator involved in HER2 expression (Wang and others 2001); STAT6, which blocks the immune response to breast cancer (Sinha and others 2005); and Fra-1, whose overexpression leads to increased invasion in breast cancer (Mizutani and others 2004). Like PEA3, Runx2 is also involved in breast cancer metastasis, specifically, metastasis to bone (Shore 2005). Its targets include collagenase-3 and BSP, which are upregulated in metastatic breast cancer cells (Shore 2005). Since it is well known that tumors can become hypoxic, it is not surprising that HIF-1 is overexpressed in primary breast tumors (Kimbro and Simons 2006). Its best known target is VEGF, an inducer of angiogenesis (Kimbro and Simons 2006). MYC is amplified and overexpressed in breast cancer (Chen and Olopade 2008). Its amplification is correlated with tumor progression and poor prognosis (Chen and Olopade 2008). MYC binds MAX to form a heterodimer that

induces the transcription of genes such as MTA1, which is involved in transformation; PEG10, which plays a role in proliferation; hTERT; and VEGF (Chen and Olopade 2008). In a transgenic mouse model, overexpression of MYC in the mammary epithelium caused breast cancer to develop after eight months (Rose-Hellekant and Sandgren 2000). Similar to MYC, MYB is amplified in hereditary breast cancer (Kauraniemi and others 2000). MYB is involved in ER-dependent breast cancer cell proliferation (Ramsay and Gonda 2008). Its targets are anti-apoptotic genes, such as MYC, cyclin A1, and BCL2 (Ramsay and Gonda 2008).

Several transcription factors are constitutively active in breast cancer, including the aryl hydrocarbon receptor, STAT3, and NF-κB (Pensa, Watson, Poli 2009; Schlezinger and others 2006; Vogel and Matsumura 2009). The aryl hydrocarbon receptor targets CYP1B1, a P450 enzyme (Schlezinger and others 2006). STAT3 is correlated with increased breast cancer cell survival, cytoskeletal reorganization, and migration (Pensa, Watson, Poli 2009). It activates HGF (Elliott and others 2002), cyclin D1, MYC, and bcl-XL (Silva and Shupnik 2007). In addition, it blocks the transcription of p21, which is an inhibitor of cell cycle progression (Silva and Shupnik 2007). Constitutively active NF-κB, which is found in more than 90% of breast cancer (Vogel and Matsumura 2009), leads to breast cancer tumors that are hormone-independent (Wysocki and Wierusz-Wysocka 2010) and drug resistant (Garg and others 2003).

Many transcription factors act as tumor suppressors, including FoxP3, KLF10, p53, and GATA3. FoxP3, an X-linked breast cancer tumor suppressor, blocks HER2 expression (Medema and Burgering 2007). KLF10 is a transcription factor whose expression is inversely correlated with breast cancer stage (Subramaniam and others 2010). Its targets are BARD1 and Smad2, which are tumor suppressors (Subramaniam and others 2010). The tumor suppressor, p53, is mutated in about 26% of all breast cancers (Patocs and others 2007). It transactivates p21 and can also transcriptionally activate Bax1, leading to apoptosis (Ingvarsson 1999). GATA3, the most highly expressed transcription factor in the mammary epithelium (Kouros-Mehr and others 2008), is normally involved in luminal epithelial cell differentiation (Chou, Provot, Werb 2010). However, it is lost during cancer progression (Chou, Provot, Werb 2010). Indeed, decreased GATA3 expression is correlated with a worse prognosis, characterized by less differentiated, ER- cancer (Chou, Provot, Werb 2010).

The steroid hormone receptors, which are ligand-activated nuclear receptors that act as transcription factors, deserve special mention when it comes to breast cancer. The estrogen receptor (ER) and the progesterone receptor (PR) are overexpressed in many breast cancers. This has led to the development of anti-estrogens and aromatase inhibitors for breast cancer treatment. Besides leading to breast cancer tumorigenesis, ER also induces breast cancer progression (Carroll and Brown 2006), and it is not only overexpression, but mutations and alternative splicing that can cause breast cancer (Toran-Allerand 2004). ER targets include PR, c-jun (Fang, Chen, Weigel 2009), p52/TFF1, MYC, cyclin D1, and BCL2 (Welboren and others 2009). Like ER, PR also contributes to breast cancer. The progesterone receptor causes cells to enter S phase and mediates anchorage-independent growth in response to progestin (Daniel, Knutson, Lange 2009). PR targets include MYC (Lange 2008), p21, EGFR, SGK, Tissue Factor, Muc-1, HB-EGF, and IRS-1 (Daniel, Knutson, Lange 2009). In addition to ER and PR in breast cancer, it is interesting to note that the androgen receptor (AR) protects against breast cancer. AR expression is correlated with a better prognosis (Yeap, Wilce, Leedman 2004), and mutations in the AR DNA-binding domain have been found in male breast cancer (MacLean, Warne, Zajac 1995).

3. ATF/CREB transcription factors in breast cancer

Like the transcription factors described in the previous section, the ATF/CREB family of transcription factors plays a role in breast cancer and may prove to be an effective therapeutic target. Some family members, such as ATF1, are protective against breast cancer, while the roles of others, such as ATF2 and ATF3, remain controversial. Still other family members, such as ATF4, ATF5, and CREB, promote breast cancer pathology (Table 1). These latter may be the most promising targets for intervention, since inhibiting their production or activation could block tumor growth and metastasis. The following sections will focus on the structure and function of individual ATF/CREB transcription factors.

4. Structure of ATF/CREB family members

The ATF/CREB family consists of a group of transcription factors that all contain an N-terminal DNA-binding domain and a C-terminal basic leucine zipper (B-ZIP) domain that binds other B-ZIP transcription factors to form homo- and heterodimers (Vinson and others 2002). ATF and CREB were both originally named in 1987 and were later found to bind to the same consensus sequence (Hai and Hartman 2001). The DNA-binding consensus sequence for this family is GTGACGT A/C A/G, which is found in the promoter region of target genes (Hai and Hartman 2001). Specificity is achieved by homo- and heterodimerization and epigenetic mechanisms, such as DNA methylation (Hai and Hartman 2001). For example, ATF1 forms heterodimers with CREM Ia and CREM IIb (Newman and Keating 2003). Likewise, ATF2, ATF4, and ATF5 all form heterodimers with C/EBPγ (Newman and Keating 2003). Based on the dimers that they form, ATF/CREB transcription factors are able to regulate the transcription of many target genes involved in breast cancer pathology and suppression.

5. ATF1

Several groups have identified ATF1 targets in both mice and humans. For example, Torti's group at Wake Forest found that ATF1 aids in the transcription of H ferritin in mouse fibroblasts (Tsuji, Torti, Torti 1998). Perhaps more relevant to breast cancer, ATF1 increases the transcription of H-2D^d, a major histocompatibility complex (MHC) class I gene (Ishiguro, Brown, Meruelo 1997). The transcription of such a gene could allow the immune system to tag breast cancer cells for destruction. Besides its effects on the immune system, ATF1 may also play a role in breast cancer via its regulation of steroidal hormone synthesis. Clem et al. (Clem, Hudson, Clark 2005) showed that ATF1 binds the steroidal acute regulatory protein (StAR) promoter, although they failed to determine whether this association activates or blocks transcription. Regardless of ATF1's effect, regulation of StAR, an enzyme necessary for estradiol synthesis, may play an important role in preventing breast cancer because a longer time of exposure to estradiol (menarche to menopause) is correlated with increased breast cancer risk. In addition to its actions on H-2D^d and StAR in mice, ATF1 blocks thrombospondin1 transcription in human thyroid cancer cells (Ghoneim and others 2007). Whether or not this effect translates to breast cancer cells has yet to be confirmed. Most relevant to breast cancer is that BRCA1 activates ATF1 (Houvras and others 2000). BRCA1 and BRCA2 act as tumor suppressor genes, and they often contain mutations in breast cancer. Houvras et al. (Houvras and others 2000) found that wild type (wt) BRCA1 bound ATF1, causing transcription of a luciferase reporter gene. Such a finding strongly suggests

ATF/CREB Family Member	Role in Breast Cancer	Targets
ATF1	Most likely supresses tumor formation	H ferritin (Tsuji, 1998) H-2D^d (Ishiguro, 1997) StAR (Clem, 2005) Thrombospondin 1 (Ghoneim, 2007)
ATF2	Unclear	Collagen, type X, α1 (Tsuchimochi, 2010) MMP13 (Tsuchimochi, 2010) Cyclin A (van Dam, 2001) Aromatase (Deb, 2006) MMP2 (Song, 2006) COX2 (Subbaramaiah, 2002) Cyclin D1 (Lee, 1999) Maspin (Maekawa, 2008) IFNγ (Xue, 2005) FoxP3 (Liu, 2009)
ATF3	Unclear	Fibronectin (Yin, 2010) Snail (Yin, 2010) Twist (Yin, 2010) Slug (Yin, 2010) av integrin (Yin, 2010) β6 integrin (Yin, 2010) E-cadherin (Yin, 2010)
ATF4	Increased malignancy Angiogenesis	Osteocalcin (St-Arnaud, 2007) Type I collagen (Ameri, 2008) TRB3 (Ameri, 2008) E-selectin (Ameri, 2008) Asparagine synthetase (Ameri, 2008) RANKL (Ameri, 2008) VEGF (Ameri, 2008) GADD34 (Fels, 2006) CHOP (Fels, 2006) Gamma-synuclein (Hua, 2009) LAMP3 (Mujcic, 2009)
ATF5	Cell Survival	Phosphoenolpyruvate carboxykinase 2 (Pascual, 2008) Aldolase B (Pascual, 2008) ID1 (Gho, 2008) Egr-1 (Li, 2009; Liu, 2011) Mcl-1 (Sheng, 2010) Bcl-2 (Dluzen, 2011) Hsp27 (Wang, 2008) CYP2B6 (Pascual, 2008)
CREB	Malignancy	Aromatase (Brown, 2010) Bcl-2 (Dong, 1999)

Table 1. The roles of ATF/CREB family members in breast cancer.

that ATF1 protects against breast cancer. The fact that ATF1 associates with BRCA1, activates H-2D^d, and may block StAR synthesis indicates that it acts as a tumor suppressor in breast cancer. On the other hand, its blockage of thrombospondin would suggest that it plays a pro-tumorigenic role. However, the work with thrombospondin has not been verified *in vivo*, and such an effect may only occur in thyroid cancer cells. Unfortunately,

very few studies have been performed on the role of ATF1 in breast cancer. Important future studies will elucidate the effects of ATF1 on immunity and hormone synthesis in both normal and neoplastic breast cells, as well as its role in breast cancer *in vivo.*

6. ATF2

The exact role of ATF2 in breast cancer is unclear. Targets for ATF2 have been found in both chickens and mice. One such target, Col10a1 (collagen, type X, α1), mediates chondrocyte differentiation (Tsuchimochi and others 2010). ATF2 also increases the transcription of matrix metalloproteinase 13 (MMP13), which may help facilitate breast cancer metastasis (Tsuchimochi and others 2010). Matrix metalloproteinases degrade the basement membrane during the metastatic cascade. So the fact that ATF2 enhances the transcription of MMP13 indicates that it may increase the likelihood of tumor metastasis. In addition, Jun-ATF2 dimers have been shown to lead to the transcription of cyclin A, which increases cell proliferation (van Dam and Castellazzi 2001), providing further evidence for a possible oncogenic role for ATF2.

In primary human adipose fibroblasts obtained from breast cancer patients, co-culture with malignant epithelial cells increased the levels of phosphorylated ATF2 (pATF2) found at the I.3/II promoter of aromatase, the enzyme responsible for estrogen synthesis (Deb and others 2006). Co-culture with the malignant cells also increased binding of pATF2 to itself, C/EBPβ, and CBP (Deb and others 2006). The fact that ATF2 aids in the transcription of a gene that increases estrogen levels makes it seem pro-tumorigenic. Furthermore, pATF2 has been shown to aid in the transcription of matrix metalloproteinase 2 (MMP2), which increases migration in H-Ras-transformed MCF10A human breast epithelial cells (Song and others 2006). Such activity indicates that ATF2 may play a role in breast cancer metastasis, if not oncogenesis. ATF2 also forms a complex with c-Jun and c-Fos that mediates HER2's induction of cyclooxygenase-2 (COX2), which itself may be carcinogenic (Subbaramaiah and others 2002). The fact that ATF2 is downstream of HER2 lends strong support to the notion that it is involved in some breast cancers. In addition, Lee et al. (Lee and others 1999) found that v-src causes ATF2 and CREB to bind the CRE/ATF site of the cyclin D1 gene, leading to transcription of cyclin D1 in MCF7 human breast cancer cells. Cyclin D1 inactivates the retinoblastoma tumor suppressor (RB), predisposing cells to malignancy (Hunter and Pines 1994; Sherr 1994). So ATF2's role here would again indicate that it acts as an oncogene.

In contrast to the above-mentioned studies, which describe ATF2 as contributing to a malignant phenotype, several groups have characterized it as protective against breast cancer. For instance, Maekawa et al. found that knockout of ATF2 increased cell number, decreased apoptosis, and increased the number of v-K-ras-induced colonies in mouse embryonic fibroblasts (MEF's) (Maekawa and others 2007). Plus, knockdown of ATF2 decreased levels of one of its targets, the breast cancer suppressor, maspin, in the mammary tumors of ATF2^{+/-} mice (Maekawa and others 2007; Maekawa and others 2008). Such findings would support the argument that ATF2 inhibits breast cancer formation. Along those lines, ATF2 has been shown to bind to the proximal element of interferon gamma (IFNγ) in MCF7 cells (Xue, Firestone, Bjeldanes 2005). Increased production and secretion of IFNγ by breast cancer cells could help the immune system destroy malignant cells before they spread, thereby inhibiting tumor growth and preventing metastasis. In a similar vein, decreased ATF2 levels have been shown to diminish the level of FoxP3, a breast cancer tumor suppressor (Liu and others 2009), lending further support to the idea that ATF2

inhibits breast cancer. However, studies in a wide range of human breast cancer cell lines are needed in order to definitively determine ATF2's role in breast cancer.

7. ATF3

Like ATF2, ATF3's role in breast cancer remains poorly delineated, although recent evidence characterizes it as an oncogene that may be involved in metastasis. Yin et al. (Yin and others 2010) found that ATF3 mediates the TGFβ-induced increase in the expression of fibronectin, twist, snail, and slug in MCF10C1a1 human breast cancer cells. In addition, ATF3 overexpression led to an increase in av and β6 integrins, as well as increased migration in MCF10C1a1 cells (Yin and others 2010). Furthermore, ATF3 caused a decrease in E-cadherin expression, as well as other genetic and morphological changes characteristic of the epithelial to mesenchymal transition (EMT) (Yin and others 2010). All of these findings support the idea tha ATF3 mediates EMT and metastasis in breast cancer. In addition, ATF3 also supports oncogenesis, as overexpression of ATF3 in MCF10C1a1 cell that were injected into nude mice increased the incidence of tumor formation (Yin and others 2010). Similarly, overexpression of ATF3 in the mammary gland myoepithelial cells of transgenic mice caused squamous metaplasia in nulliparous females and led to the formation of mammary tumors in animals that had given birth twice (Wang and others 2008). This is perhaps the most convincing evidence that ATF3 acts as an oncogene in breast cancer.

All of the above findings on ATF3 seem to establish it as an oncogene and metastasis promoter, yet some doubt remains. Einbond et al. (Einbond and others 2007) found that actein decreased cell proliferation in mouse embryonic fibroblasts (MEF's) in an ATF3-dependent manner. However, this finding may pertain only to MEF's and not to breast cancer cells. Other groups have found that the anti-neoplastic agents, doxorubicin and gemcitabine, increase ATF3 levels in human breast cancer cell lines (Hernandez-Vargas and others 2007; Mallory and others 2005). However, it remains unclear whether these drugs are acting through ATF3 or ATF3 is upregulated as part of an intracellular compensatory response. The best evidence that we have today suggests that ATF3 acts to promote tumorigenesis and metastasis. However, more studies must be conducted in order to confirm these results.

8. ATF4

Unlike ATF2 and ATF3, ATF4 is clearly pro-tumorigenic in breast cancer. Perhaps most telling, increased ATF4 levels have been found in human tumors compared to normal tissue (Ameri and Harris 2008), and several ATF4 targets indicate an oncogenic phenotype. Targets of ATF4 include osteocalcin (St-Arnaud and Elchaarani 2007), type I collagen, TRB3, E-selectin, and asparagine synthetase (Ameri and Harris 2008). More relevant to cancer, ATF4 acts as an activating transcription factor for RANKL, which activates Akt/PKB, an anti-apoptotic enzyme (Ameri and Harris 2008). Such activity in the breast would favor the formation of cancer. Besides RANKL expression, ATF4 also induces VEGF transcription (Ameri and Harris 2008), which can lead to angiogenesis at the sites of primary and secondary tumors, allowing hypoxic tumors to reach normoxia. In addition, ATF4 likely protects tumor cells form hypoxia by increasing the transcription of GADD34 and CHOP, which protect cells from hypoxic damage (Fels and Koumenis 2006). The center of a tumor often becomes hypoxic, and ATF4 may play a role in preventing hypoxia-induced cancer

cell death. Although ATF4 benefits the organism during development, bone formation, and stress, it can also act in a sinister fashion by aiding in tumor formation.

Indeed, several studies have shown a link between ATF4 levels and a more malignant genotype in human breast cancer cells. For instance, decreased ATF4 levels have been shown to cause a decrease in gamma-synuclein levels in T47D breast cancer cells (Hua and others 2009). Such a correlation with gamma-synuclein, which is up-regulated in advanced breast cancer (Bruening and others 2000), may indicate that ATF4 mediates breast tumor progression. Furthermore, hypoxia has been shown to increase LAMP3 levels in MCF7 cells via the action of ATF4 (Mujcic and others 2009). This further implicates ATF4 in tumor progression and metastasis, as LAMP3 has been shown to play a role in metastasis (Mujcic and others 2009). Interestingly, this finding suggests that hypoxic tumors may be more likely to metastasize than those with an adequate blood supply. Finally, ATF4 has been shown to mediate the osteopontin-induced increase in VEGF expression in MDA-MB-231 cells (Chakraborty, Jain, Kundu 2008). Since VEGF secretion leads to the recruitment of endothelial cells as part of the process of angiogenesis, this would suggest that ATF4 is able to help primary and secondary breast tumors survive, at least once osteopontin has activated it. Clearly, overexpression or constitutive activation of ATF4 causes breast cancer cells to become more malignant.

9. ATF5

Like ATF4, ATF5 contributes to a malignant phenotype. Targets of ATF5 include aldolase B (Pascual and others 2008), ID1 (Gho and others 2008), Egr-1 (Li and others 2009; Liu and others 2011), Mcl-1 (Sheng and others 2010), Bcl-2 (Dluzen and others 2011), and phosphoenolpyruvate carboxykinase 2 (PEPCK) (Pascual and others 2008). Up-regulation of PEPCK, a glycolytic enzyme, could indicate that ATF5 plays a role in the Warburg effect, in which cancer cells use aerobic glycolysis to generate ATP rather than oxidative phosphorylation. It is thought that this use of a less efficient means of producing ATP allows proliferating cells to more efficiently produce other needed metabolites, such as acetyl-CoA and NADPH (Vander Heiden, Cantley, Thompson 2009). In addition to increasing PEPCK production, ATF5 activates the transcription of heat shock protein 27 (Hsp27), which blocks apoptosis (Wang, Lin, Zhang 2007). Such an anti-apoptotic mechanism may lead to breast cancer oncogenesis. Furthermore, ATF5 has been shown to increase the level of CYP2B6 in human hepatoma cells (Pascual and others 2008). This P450 enzyme metabolizes cyclophosphamide, which is used to treat breast cancer. Thus, by inducing an enzyme that degrades cyclophosphamide, ATF5 may contribute not only to oncogenesis, but also to drug resistance. Based on the target genes that it up-regulates, such as Hsp27 and CYP2B6, ATF5 should be pro-tumorigenic in breast cancer.

Indeed, our recent studies indicate that ATF5 induces transcription of the pro-mitogenic early growth response factor (Egr-1) gene in MCF7 human breast cancer cells (Li and others 2009; Liu and others 2011). In addition, ATF5 also binds the Bcl-2 P2 promoter and transactivates Bcl-2, an anti-apoptotic gene, leading to breast cancer cell survival (Dluzen and others 2011). In the future, we may see ATF5 inhibitors used to treat breast cancer, as inhibition of ATF5 leads to cell death in breast cancer cells but not human breast epithelial cells (HBEC's) (Dluzen and others 2011). To this end, we have recently found that Hsp70 interacts with the N-terminal of ATF5 and protects ATF5 from both caspase- and

proteosome-dependent protein degradation (Li and others, 2011). The next step will involve using *in vivo* studies to determine the efficacy and toxicity of ATF5 inhibitors as treatments for breast cancer.

10. CREB

Similar to ATF5, CREB can contribute to malignancy of the breast. Importantly, CREB induces the transcription of aromatase in breast adipose mesenchymal cells (Brown and Simpson 2010). Increased levels of aromatase will lead to increased estrogen levels, which have been implicated in breast cancer. In fact, aromatase inhibitors, such as exemestane and anastrazole, are currently used to treat breast cancer (Goodman and others 2006). As an example of positive feedback regulation, estrogen causes CREB to bind and activate the cyclin D1 promoter (Castro-Rivera, Samudio, Safe 2001). By activating cyclin D1, which causes cells to progress through the cell cycle, activation of CREB may further contribute to carcinogenesis. In addition, dominant negative CREB has been shown to block the transcription of bcl-2 in MCF7 cells (Dong and others 1999). Since bcl-2 blocks apoptosis, this implicates CREB as being proto-oncogenic. Although good *in vitro* studies have been done on the role of CREB in breast cancer, *in vivo* studies are needed to confirm its status as a transcription factor that supports tumor growth.

11. Conclusions

A host of transcription factors regulate breast cancer, acting as both oncogenes and tumor suppressors. The ATF/CREB family is an example of a group of transcription factors involved in breast cancer development, with some family members leading to breast cancer pathogenesis and some blocking it. Therapeutic approaches that target members that are oncogenic may lead to the next generation of breast cancer therapies. A drug that inhibits those three genes without affecting other members of the ATF/CREB family could be especially powerful because it could block many downstream targets at once. An appropriate drug discovery screen would use luciferase assays of ATF 1-5 and CREB. Compounds that inhibit ATF4, ATF5, and CREB while not affecting ATF1, ATF2, and ATF3 would be considered hits. The screen could initially compare a highly metastatic breast cancer cell line, such as 410.4 cells to a normal mammary epithelial cell line, such as HC11 cells. The screen would then be confirmed in both ER⁺ (MCF7) and ER⁻ (MDA-MB-231) cells. Such a screen could lead to efficacious new breast cancer therapeutics with relatively little toxicity.

12. Acknowledgements

13. Abbreviations

Acetyl-CoA, acetyl coenzyme A; ATF/CREB, activating transcription factor/cyclic AMP response element binding; BARD1, BRCA1 associated RING domain 1; Bcl-2, B-cell

CLL/lymphoma 2; BRCA1, breast cancer 1, early onset; BRCA2, breast cancer 2, early onset; BSP, integrin-binding sialoprotein; C/EBPβ, CCAAT/enhancer binding protein, beta; C/EBPγ, CCAAT/enhancer binding protein, gamma; CHOP, DNA-damage-inducible transcript 3; CREM, cyclic AMP responsive element modulator; CYP1B1, cytochrome P450, family 1, subfamily B, polypeptide 1; CYP2B6, cytochrome P450, family 2, subfamily B, polypeptide 6; EGFR, epidermal growth factor receptor; Egr-1, early growth response 1; ELF3, E74-like factor 3 (ets domain transcription factor, epithelial specific); ER, estrogen receptor; ETS1, v-ets erythroblastosis virus E26 oncogene homolog 1 (avian); GADD34, protein phosphatase 1, regulatory (inhibitor) subunit 15A; GATA3, GATA binding protein 3; HB-EGF, heparin-binding EGF-like growth factor; HER2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian); HIF-1, hypoxia inducible factor 1; Hsp27, heat shock protein 27; Hsp70, heat shock protein 70; hTERT, human telomerase reverse transcriptase; ICAM-1, intercellular adhesion molecule 1; ID1, inhibitor of DNA binding 1, dominant negative helix-loop-helix protein; IRS-1, insulin receptor substrate 1; KLF10, Kruppel-like factor 10; LAMP3, lysosomal-associated membrane protein 3; MAX, MYC associated factor X; Mcl-1, myeloid cell leukemia sequence 1 (BCL2-related); MMP1, matrix metallopeptidase 1 (interstitial collagenase); MMP2, matrix metallopeptidase 2 (gelatinase A, 72 kDa gelatinase, 72 kDa type IV collagenase); MMP3, matrix metallopeptidase 3 (stromelysin 1, progelatinase); MMP9, matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase); MTA1, metastasis associated 1; MYB, v-myb myeloblastosis viral oncogene homolog (avian); MYC, v-myc myelocytomatosis viral oncogene homolog (avian); NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor of kappa light polypeptide gene enhancer in B cells; PDEF, SAM pointed domain containing ets transcription factor; PEA3, ets variant 4; PEG10, paternally expressed 10; RANKL, tumor necrosis factor (ligand) superfamily, member 11; SGK, serum/glucocorticoid regulated kinase; STAT3, signal transducer and activator of transcription 3 (acute-phase response factor); STAT6, signal transducer and activator of transcription 6, interleukin 4-induced; TGFβ, transforming growth factor, beta; TRB3, tribbles homolog 3 (Drosophila); VEGF, vascular endothelial growth factor.

14. References

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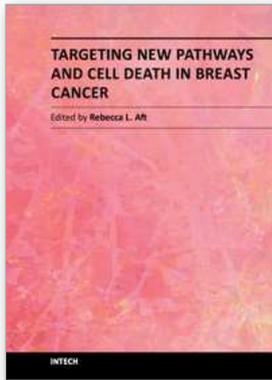
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