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Estrogen-Related Receptors and Breast Cancer: A Mini Review

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1. Introduction

The estrogen-related receptors (ERRs) α, β and γ comprise the NR3B orphan subgroup within the nuclear receptor superfamily. Although the ERRs were identified based on their sequence homology to estrogen receptor alpha (ERα), they do not bind estrogen or any other natural hormones. Recent studies have defined the roles of ERRs in the regulation of target genes at the transcriptional level as well as their participation in a broad range of physiological functions such as energy metabolism and growth progression. The expression of ERRs has been shown to be up-regulated in advanced breast cancer cells and is considered to be a negative prognostic marker for the diagnosis of the disease. This review will cover what is currently known in regards to the gene structure of ERRs in addition to their regulation, function and relationship to breast cancer.

Breast cancer is a complicated disease with 200,000 women diagnosed in the United States each year. There are many factors that influence breast cancer development and progression with hormone and nuclear receptors playing critical roles. Several reviews have been written on the emerging roles of estrogen and nuclear receptors in breast cancer (reviews (Conzen 2008; Hayashi, Niwa et al. 2009; Riggins, Mazzotta et al. 2010)). In this review we will focus on the estrogen-related receptor alpha, beta and gamma (ERRα, β and γ). ERRα and ERRβ were the first orphan nuclear receptors to be cloned in the late 1980's (Giguere, Yang et al. 1988) with ERRγ following 10 years later (Eudy, Yao et al. 1998; Hong, Yang et al. 1999; Heard, Norby et al. 2000). Although these receptors were cloned many years ago based on their sequence homology at the DNA binding domain to estrogen receptor alpha (ERα), their biological relevance (s) has only recently been uncovered (Giguere 2008; Villena and Kralli 2008) along with potential roles in cancer, and more specifically breast cancer.

1.1 Background of nuclear receptor family

ERRs belong to the orphan nuclear receptor NR3B subfamily which do not bind to any known natural ligands and are constitutively active in transcription (Benoit, Cooney et al. 2006). Crystal structure analyses of the ERRs revealed that the AF-2 containing helix 12,

essential for coactivator interaction (Nettles and Greene 2005), is in an active conformation while the ligand-binding pocket (LBP) remains empty (Greschik, Wurtz et al. 2002; Kallen, Schlaeppi et al. 2004). ERRs bind to TCAA/GGTCA elements called SFRE/ERRE and continually transactivate the target gene (Yang, Shigeta et al. 1996; Sladek, Beatty et al. 1997). While there are three members in this subfamily, both ERRβ (Zhou, Liu et al. 2006; Bombail, Collins et al. 2010) and ERRγ (Heard, Norby et al. 2000) have multiple variants that are expressed in a tissue-specific manner whereas there are no reports on variants of ERRα.

Although ERRs have high amino acid sequence homology, they are located on different chromosomes and cover a wide range of genomic space. The ESRRA gene is located at chromosome 11q13.1 (Shi, Shigeta et al. 1997) with a processed pseudogene present at 13q12.1 (Sladek, Beatty et al. 1997). It contains 7 exons and spans approximately 11 kbp genomic-space. The ESRRB gene is located at chromosome 14q24.3, has 12 exons and at least 5 variants from alternative splicing. It covers 130 kbp genomic-space ((Zhou, Liu et al. 2006; Collin, Kalay et al. 2008); Ensembl genome browser 61). The ESRRG gene spans 635 kbp genomic space, is located at chromosome 1q41 with 9 exons and 5 variants ((Eudy, Yao et al. 1998; Hong, Yang et al. 1999; Heard, Norby et al. 2000); Ensembl genome browser). A diagrammatic presentation of the relationship between ERRs and the ERs protein demonstrated that the highly conserved DNA binding domain (DBD) among the ERRs is closely related to the ERs DBD (Fig. 1). As indicated above, the ERR genes are located on different chromosomes which suggests that the gene and/or genome duplication event occurred over a long period of evolutionary time. Additionally, some of the coding exons are separated by large introns while others are clustered together.

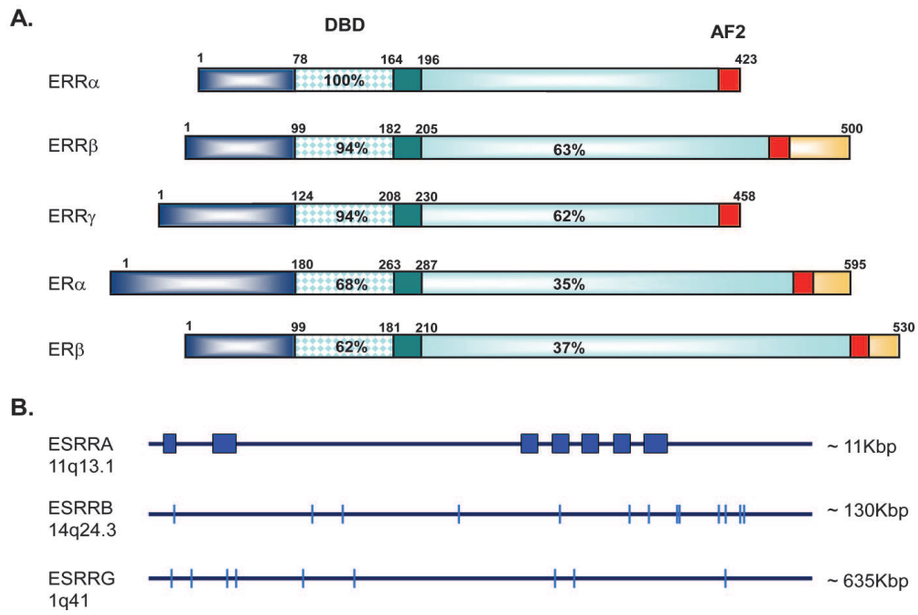

Fig. 1. A. Protein structures of the ERRs and ERs. DBD, DNA binding domain; AF2, activation function 2. Number on top indicates the amino acid position of the modular domains for the nuclear receptor. % in the box indicates the amino acid sequence homology to ERRα within the same domain. B: Gene structures of the ERRs. The size of the gene and the locations of the exons (vertical bar or box) are in approximation. Chromosome locations and the approximate gene sizes are indicated.

1.2 Expression of ERRs

Surveying the expression of all 49 nuclear receptors from 39 mouse tissues uncovered the coordination of several nuclear receptor groups with the transcriptional programs necessary to affect distinct physiologic pathways (Bookout, Jeong et al. 2006). Indeed expression of some of the nuclear receptors including the ERRs is linked to the circadian clock in key metabolic tissues suggesting their role in regulation of nutrient and energy metabolism (Horard, Castet et al. 2004; Yang, Downes et al. 2006; Giguere 2008; Villena and Kralli 2008). These studies underscore the importance of regulation and expression of nuclear receptors in normal and abnormal physiological conditions. ERRα is ubiquitously expressed in all tissues examined and is especially abundant in those with high metabolic needs such as heart, skeletal muscle and kidney (Giguere 2008). In addition, ERRα is expressed in both human and mouse embryonic stem cells (Xie, Jeong et al. 2009), during adipocyte differentiation (Fu, Sun et al. 2005) and bone morphogenesis (Bonnelye and Aubin 2002; Bonnelye, Kung et al. 2002) suggesting its roles in differentiation and development. Although expression of ERRγ is more restricted and not detectable in every tissue examined with levels that are lower than ERRα, it is still highly expressed in metabolically active tissues such as brain, skeletal muscle, heart and kidney (Zhang and Teng 2007; Giguere 2008). It was thought that ERRβ was mainly expressed in embryo (Giguere, Yang et al. 1988; Luo, Sladek et al. 1997), however as detection methods improved, ERRβ expression was found to be present in eye, brain, thyroid, kidney and the heart of adult tissues (Bookout, Jeong et al. 2006). Although ERRβ is present at lower levels as compared to ERRα and ERRγ, it also exhibited a distinct diurnal rhythmic expression much like the other two in white fat (WAT), brown fat (BAT), liver and skeletal muscle. This suggests a potential role in the coordination of oxidative metabolism in these tissues (Yang, Downes et al. 2006). The expression of ERRs in these metabolically active tissues under circadian rhythm hints to potential overlapping functions in energy metabolism.

As stated earlier, the expression level of the receptors could be closely linked to their biological function in a cell-type specific manner. This is particularly relevant for a constitutive activator since they are not regulated by the addition of ligands. Therefore the function of ERRs could be controlled by their expression level; however information regarding the mechanisms and signals that regulate their expression is limited.

1.3 Regulation of ERRs

1.3.1 Estrogen regulation of ERRs

ERRα was demonstrated to be the target gene for estrogen in the mouse uterus (Shigeta, Zuo et al. 1997) 15 years ago. Later, a combinatorial estrogen response element which can bind several nuclear receptors termed multiple hormone response element (MHRE) was identified in the human ERRα gene promoter (Liu, Zhang et al. 2003). Under the influence of estrogen, the estrogen receptor alpha (ERα), (but not the estrogen receptor beta (ERβ)) was recruited to the chromatin of the human ERRα promoter which interacted with the MHRE in an indirect tethering manner and transactivated the promoter (Liu, Zhang et al. 2003; Hu, Kinyamu et al. 2008). Surprisingly, in a similar experiment conducted with ER negative SKBR3 cells, estrogen treatment also induced chromatin modification around the MHRE region and recruited the coregulators and RNA polymerase II to the ERRα promoter (Li, Birnbaumer et al. 2010). This suggests that the ERRα gene can be regulated by estrogen in a non-ER dependent manner. Indeed, the MHRE (a 57 bp region in human and a 34 bp region) in mouse of the ERRα gene is a pleiopropic response element for multiple nuclear receptors

(Liu, Zhang et al. 2005) and also serves as the binding site for ERRα and ERRγ (Laganiere, Tremblay et al. 2004; Mootha, Handschin et al. 2004; Liu, Zhang et al. 2005). ERRγ was recently found to be responsive to estrogen, its expression able to be stimulated in a dose dependent manner. Furthermore, this response can be blocked by the pure estrogen antagonist ICI 182,780 (Ijichi, Shigekawa et al. 2011). By using chromatin immunoprecipitation (ChIP)-on chip analysis with MCF-cells, a number of potential EREs in the second intron of the human ERRγ gene were previously identified (Carroll, Meyer et al. 2006). These studies demonstrated a functional cross-talk between ERs and ERRs in the estrogen signaling pathway.

1.3.2 PCG-1α regulation of ERRα

While nuclear receptor binding to its target gene is important for transcriptional activation, it requires specific interactions with coregulatory proteins (Glass, Rose et al. 1997; McKenna, Lanz et al. 1999). One of the key regulators in energy metabolism is peroxisome proliferator-activated receptor γ coactivator -1α (PGC-1α). PGC-1α not only interacts with and stimulates ERRα transcriptional activity, it also enhances its expression in an autoregulatory loop mechanism (Schreiber, Knutti et al. 2003; Laganiere, Tremblay et al. 2004; Mootha, Handschin et al. 2004; Zhang and Teng 2007; Wang, Li et al. 2008). By combining PGC-1α induced genome-wide transcriptional profiles with a computational strategy to detect cis-regulatory motifs approach, ERRα was discovered to be a key transcription factor that is involved in cross-talk with PGC-1α in regulating the oxidative phosphorylation pathway (Mootha, Handschin et al. 2004). PGC-1α is capable of co-activating nearly all known nuclear receptors and many other transcription factors (Puigserver and Spiegelman 2003), yet it possesses a unique protein interaction surface that is dedicated specifically to the ERRs (see review and references therein (Villena and Kralli 2008)). With this unique relationship, ERRα expression is co-regulated with PGC-1α under various physiological stimuli such as during fasting (Ichida, Nemoto et al. 2002), under cold exposure (Schreiber, Knutti et al. 2003) and exercise (Cartoni, Leger et al. 2005). Therefore, induction of PGC-1α expression by physiological stimuli also induces ERRα expression in a positive feed-forward mechanism. The expression level of ERRα is also affected by ERRγ (Liu, Zhang et al. 2005; Zhang and Teng 2007) and cAMP (Liu, Benlhabib et al. 2009). These studies showed that multiple mechanisms are involved in the regulation of ERRs expression and function.

1.4 Function of the ERRs

1.4.1 ERRs interactions with ERs and other nuclear receptors

Understanding the role of ERRs in ER-mediated function starts with their cloning. ERRα and ERRβ were identified based on a search for genes with sequence homology at the DNA binding domain to ERα (Giguere, Yang et al. 1988). Eight years later, ERRα was re-cloned as a specific binding protein to an extended hormone response element (HRE) half-site, the TCAAGGTCATC region of the human lactoferrin gene promoter (Yang, Shigeta et al. 1996). This finding revealed that ERRα binds to the steroidogenic factor 1 (SF-1) binding element termed SFRE and later renamed this element to ERRE as estrogen-related receptor response element whenever addressing the ERRs binding (Sladek, Bader et al. 1997). It was demonstrated that binding of ERRα to this ERRE enhances the ER-mediated estrogen response of the lactoferrin gene (Yang, Shigeta et al. 1996). ERRα was later shown to bind a variety of EREs as a monomer or homodimer (Johnston, Liu et al. 1997; Vanacker, Pettersson et al. 1999; Zhang and Teng 2000; Zhang and Teng 2001) and genes possessing such ERE or

ERRE or both were subject to ERRα regulation (Sladek, Beatty et al. 1997; Vega and Kelly 1997; Vanacker, Bonnelye et al. 1998; Vanacker, Delmarre et al. 1998; Sumi and Ignarro 2003). Other than the binding elements, ERRs and ERs recognize similar co-activators and co-repressors (Xie, Hong et al. 1999; Zhang and Teng 2000). Therefore, an extensive cross-talk between the ERRα and ERα occurs at the multiple steps of the transcriptional process ((Giguere 2002) and references therein). Depending on the EREs and the surrounding elements, ERRα could either enhance or inhibit the estrogen responsiveness of the target genes (Yang, Shigeta et al. 1996; Kraus, Ariazi et al. 2002; Zhang, Chen et al. 2006).
ERRβ represses glucocorticoid receptor (GR) activity (Trapp and Holsboer 1996) and inhibits the function of NF-E2 Related Factor 2 (Nrf2) on antioxidant response element mediated gene expression (Zhou, Lo et al. 2007) in a cell-specific manner. Recently, variant isoforms (Long and Short) of ERRβ were found in the human endometrium. Increasing the expression of the Long form enhanced the ERα-mediated stimulation of c-myc expression and cell proliferation in Ishikawa cells whereas the Short form had no effect (Bombail, Collins et al. 2010). Interestingly, ERRγ (but not ERRα or ERRβ) was shown to activate the orphan nuclear receptor small heterodimer partner (SHP; NR0B2) (Sanyal, Kim et al. 2002) and the dosage-sensitive sex reversal (DAX-1) promoter (Park, Ahn et al. 2005). ERRs could bind to the promoter of other nuclear receptors such as thyroid hormone receptor (TR) (Vanacker, Bonnelye et al. 1998; Castet, Herledan et al. 2006), PPARα (Huss, Torra et al. 2004), RXRα and RXRβ (Sonoda, Laganiere et al. 2007) thus potentially regulating their expression. These nuclear receptors are also involved in a wide range of physiological functions. Therefore, the cross-talk of ERRs with other nuclear receptors expands their functional roles and points to the importance of their expression in normal and diseased conditions.

1.4.2 The role of ERRs in homeostasis

A major advance in understanding the role of ERRα in energy homeostasis comes from the observation that the medium-chain acyl-coenzyme A dehydrogenase (MCAD) is an ERRα target (Sladek, Bader et al. 1997; Vega and Kelly 1997). The MCAD is an enzyme that mediates the first step in the mitochondrial β-oxidation of fatty acids (Schulz 1991). This was followed by the discovery of a close relationship between ERRα and PGC-1α in transcriptional regulation (Huss, Kopp et al. 2002; Ichida, Nemoto et al. 2002; Schreiber, Knutti et al. 2003). Evidence indicates that PGC-1α serves as a key regulator of mitochondrial biogenesis in mammals. This includes the activation of the transcription of mitochondrial uncoupling protein -1 (UCP-1) and the induction of the expression of NRF-1, NRF-2 and Tfam, all critical factors for mitochondrial function and maintenance. Furthermore, PGC-1α up-regulates the expression of genes involved in mitochondrial fatty acid oxidation and triggers mitochondrial proliferation (see review (Kelly and Scarpulla 2004)). The regulatory roles of PGC-1α in these key metabolic processes were mediated by ERRα (see review and references therein (Giguere 2008; Villena and Kralli 2008)). In microarray studies, over expression of PGC-1α in culture cells induced hundred of genes encoding mitochondrial proteins involved in fatty acid oxidation (FAO), the tricarboxylic acid cycle (TCA), oxidative phosphorylation (OXPHOS), mitochondrial membrane and carbohydrate metabolism. Interestingly, these PGC-1α effects can be blocked by siRNA against ERRα or be induced by over expression of constitutively active ERRα (Mootha, Handschin et al. 2004; Schreiber, Emter et al. 2004). Taken together, ERRα plays a major role

in the regulation of sets of genes involved in a wide range of energy balance activities such as lipid transport, fatty acid oxidation, TCA cycle, oxidative phosphorylation, and mitochondrial biogenesis to name a few.

2. ERRs in breast cancer

Searching for therapeutic targets in cancer biology is an important endeavor and the nuclear receptor has been shown to be one such target. Recently, the expression profile of 48 nuclear receptors in 51 human cancer cell lines derived from nine different tissues from the NC160 collection was investigated (Holbeck, Chang et al. 2010). The results uncovered a number of potential receptor-drug interactions and demonstrated that the individual receptor levels may predict a response to therapeutic intervention. Like all cancers, breast cancer is a complicated disease and many factors, estrogen in particular, contributes to its development and progression (Kelsey and Bernstein 1996). Although estrogen action is mediated through two receptors (ERα (Greene, Gilna et al. 1986) and ERβ (Kuiper, Enmark et al. 1996)), 70% of breast cancers express ERα which serves as the mediator for estrogen action (Russo, Hu et al. 2000; Conzen 2008; Hayashi, Niwa et al. 2009). In view of the structural similarity and functional cross-talk of the ERs and ERRs, it is possible that ERRs are also involved in breast cancer biology (review and references therein (Ariazi and Jordan 2006; Riggins, Mazzotta et al. 2010)).

2.1 ERRs as potential biomarkers

Using qPCR to measure the mRNA levels of ERs, epidermal growth factor receptor, ErbB family members, and ERR mRNA levels in 38 unselected primary breast tumors and 9 normal mammary gland epithelial cells from breast reduction surgery revealed that ERRα is highly expressed in a subset of tumors with elevated levels of ErbB2, an indicator of aggressive tumor behavior and nonfunctional ERα. Unlike ERRα, expression of ERRγ in breast tumors correlates with ER-positive status and ErbB4 expression which is a preferred clinical marker. These studies suggest that ERRα can be used as an unfavorable whereas ERRγ can serve as a favorable marker for diagnosis of clinical outcome. The mRNA level of ERRβ in the above mentioned breast tumor samples is very low and the potential as a biomarker unclear (Ariazi, Clark et al. 2002). Despite the proposed use of ERRγ as a favorable marker, over expression of ERRγ contributed to the development of tamoxifen (TAM)- resistance in cell lines derived from invasive lobular carcinoma (Riggins, Lan et al. 2008). Additional studies using an immunohistochemistry approach combined with RT-PCR supports the earlier findings that ERRα expression in breast carcinoma is associated with an increased risk of recurrence and an adverse clinical outcome (Suzuki, Miki et al. 2004).

2.2 ERRα and breast cancer cell growth

ERRα has been extensively studied in the context of breast cancer (Ariazi, Clark et al. 2002; Suzuki, Miki et al. 2004; Barry and Giguere 2005; Ariazi and Jordan 2006; Ariazi, Kraus et al. 2007; Stein, Chang et al. 2008; Chisamore, Wilkinson et al. 2009; Deblois, Hall et al. 2009; Stein, Gaillard et al. 2009; Dwyer, Joseph et al. 2010). Correlation between the expression of ERRs and disease outcome presents a first glimpse of the potential role of ERRs in breast cancer. Further studies using an unbiased microarray approach to understand the cross-talk between ERs and ERRs in MCF-7 cells yielded unexpected results (Stein, Chang et al. 2008). Despite the functional cross-talk between ERs and ERRs presented earlier, ERRα was found

to regulate a smaller set of genes that overlapped with ERα despite regulating many more genes not involved in estrogen signaling. Analysis of the microarray data from ER-regulated and ERR-regulated genes in MCF-7 cells by gene ontology (GO) showed that the majority of genes regulated by ERRα are involved in energy metabolism, oxidative stress and detoxification as expected. Interestingly, ERRα also induces vascular endothelial growth factor (VEGF), a highly angiogenic factor. Importantly, knockdown ERRα expression in MDA-MB-231 cells reduced tumor cell migration *in vitro* and tumor growth as xenografts *in vivo* (Stein, Chang et al. 2008). Further studies demonstrated that ERRα-dependent activation of VEGF mRNA expression occurs in several different breast cancer cell lines (Stein, Gaillard et al. 2009). This suggests that ERRα promotes tumor cell growth by stimulating VEGF expression. These studies together with the finding that ERRα also induces the pro-migratory factor, WNT11 (Dwyer, Joseph et al. 2010) provides a basis for highly expressed ERRα to be considered an overall negative phenotype of breast cancers.

2.3 ERRα and aromatase

As indicated above, there is much evidence that points to potential mechanisms of how ERRα influences breast cancer biology. ERRα plays a role in the local production of estrogen in breast cancer cells with levels in tumor tissue being several-fold higher than in normal circulating estrogen (Thorsen, Tangen et al. 1982; van Landeghem, Poortman et al. 1985) and aromatase, a key enzyme in converting androgens to estrogens, is also up-regulated in tumor cells (Miller and O'Neill 1987; Sasano and Harada 1998; Chen, Zhou et al. 1999). The presence of aromatase mRNA in the intra-tumoral location of 19 breast carcinoma tissues was detected using laser capture microdissection (LCM) and quantitative reverse transcription-PCR (q-PCR) while aromatase protein was verified by immunohistochemistry (Miki, Suzuki et al. 2007). Furthermore, microarray expression profiling of aromatase and ERRα mRNA in isolated carcinoma cells demonstrated a significant positive correlation (Miki, Suzuki et al. 2007). Although regulation of aromatase expression is tissue- and promoter-specific, its activity in breast carcinoma is higher than in normal tissue of the same patients (Silva, Rowlands et al. 1989; Miller, Anderson et al. 1990; Lipton, Santen et al. 1992). This suggests that the regulation of aromatase expression in breast cancer cells of the patient has been changed. Indeed, promoter switching in breast cancer tissue has been reported (Chen, Zhou et al. 1999; Chen, Reierstad et al. 2009) and ERRα plays a positive role (Yang, Zhou et al. 1998; Miao, Shi et al. 2010). Taken together, ERRα functions as a key modulator of intratumoral estrogen production in human breast carcinoma by stimulating the expression of the androgen-estrogen key converting enzyme, aromatase via tumor specific promoter usage.

2.4 ERRα and EGFR

ERRα has a close relationship with the ErbB2/epidermal growth factor receptor (EGFR) signaling pathway. ErbB2 is a receptor tyrosine kinase and in combination with EGFR, activates a complex array of downstream signaling pathways which leads to phosphorylation of multiple transcription factors including ERRα. Phosphorylation of these transcription factors promotes growth and proliferation (reviewed in ref. (Yarden and Sliwkowski 2001)). Upon EGF treatment, ERRα in MCF-7 cells was phosphorylated and preferentially recruited to the pS2 promoter. Furthermore, phosphorylated ERRα showed enhanced DNA binding capability in an *in vitro* study (Barry and Giguere 2005). Additionally, mitogen-activated protein kinases (MAPK) and Akts (components of the

ErbB2 pathway) are involved in ERRα phorphorylation and transactivation since inhibitors to MAPK and Akt also block ERRα target gene activation (Ariazi, Kraus et al. 2007). These observations suggest that ERRα phosphorylation provides a mechanism of enhanced transactivation function in breast cancer cells. Recently, using a mouse model of ErbB2-initiated mammary tumorigenesis found that ablation of ERRα significantly delays ErbB2-induced tumor development, lowers the levels of ErbB2 and co-amplifies transcripts within the 17q12-21 chromosomal region (the ErbB2 amplicon) (Deblois, Chahrour et al. 2010). The minimal 17q12 amplicon houses not only the ErbB2 gene; it also includes those involved in signal transduction, transcription, cell migration and invasion, inhibition of apotosis, genomic instability and tamoxifen resistance. ERRα binds to those genes and directs the recruitment of co-activators PGC-1β and RNA polymerase II to their promoters (Deblois, Chahrour et al. 2010). Furthermore, ERRα antagonists repress the effect of ERα on the ErbB2 promoter which leads to the development of tamoxifen resistance in breast cancer cells.

2.5 ERRα and AIB1

Comparing the co-activators along with the expression of various nuclear receptors in 48 primary breast tumor samples, a positive correlation between ERRα and AIB1 (amplified in breast cancer-1) (Anzick, Kononen et al. 1997) was found. AIB1 is an oncogenic co-activator of ERα that is frequently amplified and over expressed in human breast carcinomas (Anzick, Kononen et al. 1997; Liao, Kuang et al. 2002). In addition, these two proteins were abundant in the tumor samples and a direct interaction of the receptor and co-activator was demonstrated by fluorescence-resonance energy transfer, mammalian two-hybrid, and coimmunoprecipitation assay with endogenous proteins. On the other hand, the levels of PGC-1α (a well characterized ERRα co-activator) in primary breast carcinoma was low and no detectable association with ERRα was found (Heck, Rom et al. 2009). The enhanced association of ERRα with AIB1 underscores the functional significance of ERRα/AIB1 rather than the ERRα/PGC-1α interaction for breast tumor development and progression.

2.6 ERRγ and PGC-1β

Although direct evidence between cellular metabolism and breast cancer development is lacking, switching from aerobic oxidative phosphorylation to glycolytic metabolism is a typical feature of cancer cells (Warburg 1956). Recent reports demonstrated that the expression of miR-378, an ErbB2-regulated microRNA, correlates with the progression of human breast cancer by inducing the metabolic shift from an oxidative to a glycolytic pathway (Eichner, Perry et al. 2010). The miR-378 is embedded within PGC-1β and when expressed, inhibits the expression of ERRγ and GABPA (PGC-1β partners), a function that is opposite to the PGC-1 family of co-activators. In view of the close relationship of ERRs and PGC-1 coactivator family in the context of energy metabolism (Giguere 2008; Villena and Kralli 2008), the finding that miR-378 targets ERRγ but not ERRα demonstrated again that the isoforms of ERR possess differential functions as well as overlapping activities either in regulating energy or in breast cancer biology.

3. The potential agonist and antagonist of ERRs

As mentioned earlier, the ERR-coactivator or corepressor interaction determines the receptor's functional activity. Any factor that interrupts this interaction has the ability to modulate ERR function (Huss, Kopp et al. 2002; Kamei, Ohizumi et al. 2003; Schreiber, Knutti et al. 2003;

Debevec, Christian et al. 2007), therefore could be a potential therapeutic target site. Small-molecule agonists for ERRβ and ERRγ have been identified and characterized. However, identifying an agonist for ERRα has proved to be difficult (Yu and Forman 2005; Hyatt, Lockamy et al. 2007). Nonetheless, novel synthetic antagonists of ERRs, especially for ERRα, are emerging (Yang and Chen 1999; Coward, Lee et al. 2001; Tremblay, Bergeron et al. 2001; Tremblay, Kunath et al. 2001; Busch, Stevens et al. 2004; Willy, Murray et al. 2004; Chisamore, Cunningham et al. 2009). By disrupting the constitutive ERR/co-activator interaction or by inducing proteosome-dependent protein degradation of the receptor, these small molecules inhibit the function of ERRs and thus tumor growth and progression (Ariazi and Jordan 2006; Stein, Chang et al. 2008; Chisamore, Wilkinson et al. 2009; Heck, Rom et al. 2009; Wu, Wang et al. 2009). Recently, a series of diaryl ether-based ligands for ERRα were developed and demonstrated in animal models to be antidiabetic agents (Patch, Searle et al. 2011). Taken together, these studies provide a basis for the further development of therapeutics to treat breast cancers based on suppressing ERRα expression and activity. Recently, environmental estrogenic compounds were found to modulate ERRα (Suetsugi, Su et al. 2003) and ERRγ (Matsushima, Kakuta et al. 2007; Takashima-Sasaki, Mori et al. 2007; Wang, Fang et al. 2009; Hirvonen, Rajalin et al. 2011) activities in either a positive or negative manner. The impact of environmental factors on breast cancer via ERRs is currently unclear.

4. ERRs in other cancers

Since the over expression of ERRα in breast cancer was discovered (Ariazi, Clark et al. 2002; Suzuki, Miki et al. 2004), additional studies have found an association between the abnormal expression of ERRs and a variety of tumors and cancers such as prostate (Cheung, Yu et al. 2005; Yu, Wang et al. 2007; Yu, Wong et al. 2008), ovarian (Sun, Sehouli et al. 2005), colon-rectal (Cavallini, Notarnicola et al. 2005) and endometrium (Gao, Sun et al. 2006). In neoplastic prostatic tissues, ERRβ and ERRγ show levels that are either reduced or undetectable as compared to normal prostatic epithelial cells (Cheung, Yu et al. 2005). This suggests a down-regulation of these two receptors in prostate cancer. In a series of experiments, the forced induction of ERRβ or ERRγ in androgen sensitive (LNCaP) and androgen-insensitive (DU145) prostate cancer cells demonstrated that over expression of these two receptors suppresses cell proliferation and tumorigenicity of the cancer cells. The inhibition of prostate cancer cell proliferation was due to cell cycle arrest as demonstrated by the induction of cyclin-dependent kinase inhibitor p21 by ERRβ and p21/p27 by ERRγ. Moreover, ERRβ and ERRγ-mediated growth inhibition could be potentiated by their specific agonist DY131 and reduced by siRNA (Yu, Wang et al. 2007; Yu, Wong et al. 2008). The expression of ERRβ and ERRγ in prostate cancer is in contrast to ERRα in breast cancer cells, colorectal tumor, and malignant colon cells (Cavallini, Notarnicola et al. 2005). ERRα expression in endometrial adenocarcinoma is positively correlated with myometrial invasion while a negative correlation was observed between the expression of ERRγ mRNA and nodal metastasis (Gao, Sun et al. 2006). Therefore, the expression levels of the subtype ERRs in cancer cells provides a potential prognostic strategy for the therapeutic treatment of the cancer.

5. Conclusion

The studies cited in this review demonstrate that ERRs are differentially expressed in normal and cancer cells. While many factors influence their expression, ERRs in turn,

regulate many sets of genes involved in a wide variety of signaling pathways. As of today, the majority of studies are on ERRα and its relationship with breast cancer development and progression. How ERRα is involved in breast cancer biology is summarized in Figure 2.

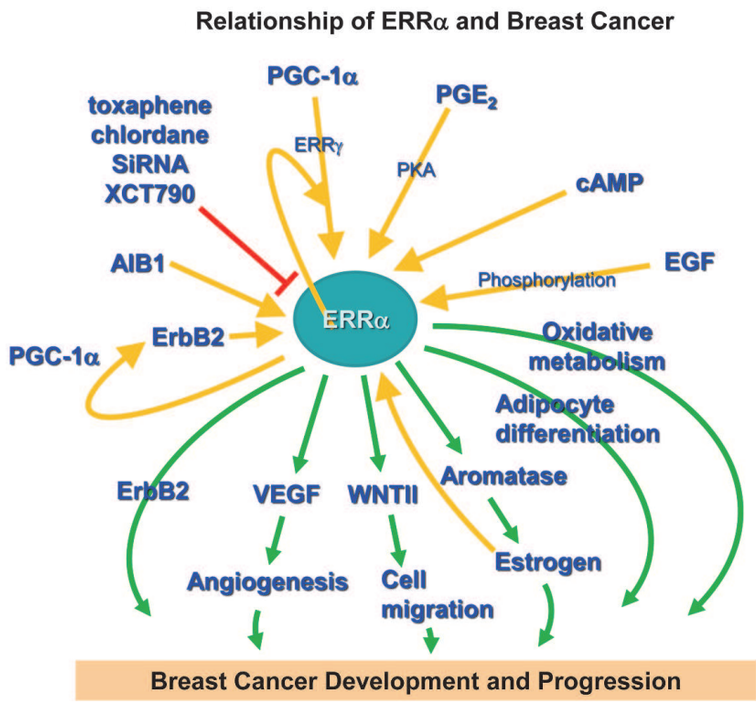

Fig. 2. Potential pathways that regulate ERRα expression and influences breast cancer development and progression. Yellow arrow, upregulates ERRα expression; red arrow, downregulates ERRα activity; green arrow, potential mechanisms of ERRα action on breast cancer.

The roles of ERRγ in breast cancer have yet to be established. While ERRγ targets the same metabolic gene network as ERRα, it may perform distinct physiological functions such as participation in the metabolic shift pathway in breast cancer cells. ERRγ was recently demonstrated as a target for endocrine disruptors, the estrogen-mimic of the environmental chemicals which may be involved in breast cancer development or progression. Compared to ERRα and ERRγ, the number of functional studies on ERRβ has been relatively slim. Nonetheless, the report on the repressive function of ERRβ in prostate cancer cells will certainly garner additional attention to this orphan receptor. Collectively, the role of these ERRs in this disease state is emerging and they could prove to be a viable therapeutic target in the treatment of breast cancer.

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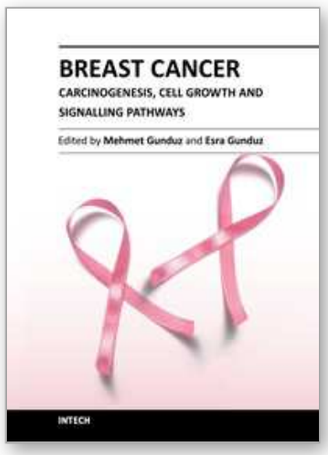

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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