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Review

ERRs and cancers: Effects on metabolism and on proliferation and migration capacities☆

Stéphanie Bianco[1], Juliette Sailland, Jean-Marc Vanacker*

Institut de Génomique Fonctionnelle de Lyon, Université de Lyon, Université Lyon 1, CNRS, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69364 Lyon cedex 07, France

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ABSTRACT

ERRs are orphan members of the nuclear receptor superfamily which, at least for ERRα and ERRγ display important roles in the control of various metabolic processes. On other hand, correlations have been found between the expression of ERRα and γ and diverse parameters of tumor progression in human cancers. Whereas it is tempting to speculate that ERR receptors act in tumors through the regulation of metabolism, recent data have suggested that they also may directly regulate tumor proliferation and progression independently of their effects on metabolism. The two aspects of tumoral functions of ERR receptors are the purpose of the present review.

Contents

1. The ERR receptor subfamily

ERRs (Estrogen-Receptor Related receptors or Estrogen-Related Receptors) α, β and γ (NR3B1–3) are members of the nuclear receptor superfamily which act as ligand-dependent transcription factors. However, no natural ligand has been identified to date for any of the ERRs which are therefore referred to as orphan receptors (reviewed in [1,2]). Moreover, crystallographic (at least for ERRα and γ) and cell-based studies have suggested that these receptors actually act in a constitutive manner [3,4]. However, several synthetic compounds have been identified that act as specific agonists or inverse agonists of a given ERR species, providing convenient tools to study their functions and allowing to envision a pharmacological approach to modulate their activities [5–10].

ERRα and β were initially isolated based on the close proximity of their DNA binding domain to that of the Estrogen Receptor alpha (hence their name) [11]. In spite of this proximity, ERRs bind to and activate transcription through specific response elements (ERR-response elements, ERREs) which are distinct from those mediating the estrogenic response (Estrogen Response Elements, EREs) [12–14]. However a small number of DNA sites bound and activated by both ERRα and ERα have been identified in breast cancer cells by transcriptome analysis and chromatin immunoprecipitation approaches on a genome-wide scale suggesting a limited extent of functional interferences between both receptors [14,15]. Coregulation by ERRα and ERα mainly affects promoters comprising mixed DNA sequences (ERE and ERRE embedded in each other) or in which both REs are located in close proximity to each other. This is for instance the case of the pS2/TTF1 gene, a human breast cancer marker, the expression of which can be stimulated by both receptors [16]. On other hand, ERα and ERRα may also regulate gene expression through binding to common ERREs as

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* Corresponding author. Tel.: +33 047 272 8591; fax: +33 047 272 8080.
E-mail address: jean-marc.vanacker@ens-lyon.fr (J.-M. Vanacker).
[1] Present address: Département de Biologie, Faculté des Sciences, Université de Sherbrooke, Sherbrooke, Québec J1K 2R1, Canada.

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Table 1
Expression of ERR receptors in tumors.

Tumor origin	ERRα	ERRβ	ERRγ
Ovary [27]			
Expression	High	n.d.	High
Correlated to	Reduced survival		Prolonged survival
Colon [22]			
Expression	High	n.d.	Low (no difference normal/cancer)
Correlated to	Higher grade		
Endometrium [21]			
Expression	High	Low	Low
Correlated to	Grade and invasion		
Prostate [23,25,30]			
Expression	High	Low	Low
Correlated to	Advanced cancer	Begnin foci	Normal and low grade cancer
Breast [26,29]			
Expression	High	?	Middle
Correlated to	Poor prognosis		Favorable outcome

n.d.: not detected.
References are indicated for each tumor origin.

exemplified for the osteopontin gene [17]. ERRα has also been suggested to interfere with androgen signaling in prostate cancer cells, through the regulation of common target genes such as PSA or Nkx3.1 [18], although the extent to which this phenomenon occurs has not been determined. Altogether this suggests that ERR receptors in general, and ERRα in particular, may play a role in estrogen/androgen-related pathologies, at least partly through the interferences they display with steroid signaling. They thus may be good candidates for the design of alternative therapies in pathologies that involve deregulation of estrogen or androgen signaling, such as hormone-dependent cancers [19,20]. However, even in these pathologies, the activities of the ERR receptors may be unrelated to steroid signaling and mainly involve their binding to ERREs.

2. ERRs and cancers

The expression of ERR receptors has been determined in various cancer types at the RNA or protein level (summarized in Table 1). ERRβ and γ are weakly (if at all) detected in endometrial and colorectal tumors [21,22]. Their expression is also low in prostate cancer cell lines and lesions, as compared to immortalized prostate cells, suggesting a negative impact of ERRβ and γ on cancer progression [23–25]. In contrast, expression of ERRγ was found higher in tumors of ovarian and mammary origin than in the corresponding normal tissue although this high expression correlates with favorable outcome and increased survival [26,27]. However this view is challenged by the suggestion that ERRγ mediates resistance to tamoxifen (an anti-estrogen widely used in breast cancer therapy) in a cellular model of invasive lobular breast carcinoma [28].

On the contrary, high expression of ERRα is globally associated with a poor prognosis in tumors originating from the colon, endometrium, ovary, prostate and breast [21–23,26,27,29,30]. Consistently, ERRα has been shown to be critical for the growth of xenografted ERα-negative, highly aggressive breast cancer cells [15]. Gene profiling in breast tumors has also indicated that the expression of direct ERRα target genes segregates with tumor subtypes implicating the receptor as a likely determinant of breast cancer heterogeneity [14]. The mechanisms leading to dysregulated ERR expression in tumors have not been investigated to date.

Altogether these data suggest that ERR receptors play important roles in tumors of various origins.

3. ERRs as regulators of energy demand

A number of physiological functions of each of the three ERRs have been deciphered. ERRβ regulates placental formation [31], maintenance of pluripotency in embryonic stem cells [13,32] and the fate of endolymph-producing cells of the inner ear [33]. *In vivo* and *in vitro* experiments have shown that the absence of ERRα or γ enhances the differentiation of mesenchymal stem cells (MSCs) into osteoblasts (bone-forming cells) [34–36, reviewed in 37]. Conversely, differentiation of MSCs in adipocytes is reduced in the absence of ERRα or γ [38,39] suggesting the involvement of these receptors in the choice of differentiation by MSCs. Several reports have also demonstrated that (at least) ERRα is involved in the functions of differentiated MSCs. This includes the control of the mineralization operated by osteoblasts [34,35] as well as the regulation of energy metabolism exerted by adipocytes (reviewed in [40,41]). ERRα positively controls lipid uptake, fatty acid oxidation, tricarboxylic acid (TCA) cycle, oxidative phosphorylation as well as mitochondrial biogenesis and function [42–48]. Fig. 1 displays a summary of these activities. The receptor exerts these effects directly through binding to the promoter of target genes (as demonstrated by ChIP experiments), or indirectly through the induction of the expression of NRF1, GABPα and PPARα [46,49]. Most if not all of these activities appear to depend on members of the PGC-1 coactivator family (PGC-1α, -β and PRC) [50–53] which on other hand also positively impact on the autoregulatory loop controlling ERRα expression at the promoter level [54]. Noteworthy, the metabolic control exerted by ERRα also extends to other cells/tissues displaying high energy requirement, such as cardiomyocytes or macrophages [48,55]. Although the metabolic functions of ERRγ are less documented, it has been shown that this receptor plays instrumental roles in oxidative metabolism in the heart and skeletal muscle, regulating an array of target genes [12,56,57]. Interestingly, many, but not all, of these genes are also transcriptionally modulated by ERRα. In conclusion ERRs (at least ERRα and γ) can be viewed as energy sensors, required for cell adaptation to various stresses and demands. Since tumor cells need high energy amounts, one of the ways through which the ERR receptors act in cancer cells may be that they regulate energy availability required by tumor cells. In agreement with this hypothesis, ERRα has been shown to regulate the expression of genes involved in the regulation of energy metabolism also in cultured mammary tumor cells [14,15] and to control oxidative phosphorylation in cell lines derived of thyroid carcinoma [58]. Furthermore, enhanced ERRα, PGC-1α and -β expression as well as of their metabolic target genes have been demonstrated in a tumor cell model for breast cancer brain metastasis as compared to parental blood circulating cells [59]. This was set in correlation with the elevated TCA cycle and fatty acid β-oxidation in the metastatic cells. However this correlation may be restricted to this particular model of brain metastasis. Indeed most cancer cells rely on anaerobic glucose metabolism (glycolytic pathway) rather than on oxidative