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Review

ERβ in breast cancer—Onlooker, passive player, or active protector?

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ABSTRACT

The role of estrogen exposure in breast cancer risk is well-documented, and both estrogen synthesis and actions through the estrogen receptor (ER) have been targeted by therapies to control hormone-dependent breast cancer. The discovery of a second ER form and its therapeutic implications sparked great interest. Both the original ERα and the more recently identified ERβ subtypes bind and respond similarly to many physiological and pharmacological ligands. However, differences in phytoestrogen binding have been noted, and subtype-specific ligands have been developed. Cell-based assays show that ERβ and its variants are generally less active on gene transcription than ERα, and may influence ERα activity; however, both gene- and cell-specific responses occur, and nongenomic activities are less well explored. Specific ligands, and methods to disrupt or eliminate receptor subtype expression in animal and cell models, demonstrate that the ERs have both overlapping and distinct biological functions. Overall, in cell-based studies, ERα appears to play a predominant role in cell proliferation, and ERβ is suggested to be antiproliferative.

The potential for distinct populations of breast tumors to be identified based on ER subtype expression, and to exhibit distinct clinical behaviors, is of greatest interest. Several studies suggest that the majority of ER-positive tumors contain both subtypes, but that some tumors contain only ERβ and may have distinct clinical behaviors and responses. Expression of ERβ together with ERα favors positive responses to endocrine therapy in most studies, and additional studies to determine if the addition of ERβ to ERα as a tumor marker is of clinical benefit are warranted. In contrast, the positive association between ERβ and HER2 expression in high-grade ERα-negative breast cancer does not favor positive responses to endocrine therapy. Expression of ERβ in specific clinical subpopulations, and the potential for therapies targeting ERβ specifically, is discussed.

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1. Introduction

The steroid hormone 17β-estradiol (E2) plays an important role in the development and growth of the mammary gland during puberty, pregnancy, and lactation, as well as cell proliferation under both physiological and pathophysiological states [1]. Increased time of E2 exposure, including early menarche and later menopause, is associated with increased risk of breast cancer, and may contribute to tumor growth [2,3]. E2 treatment stimulates breast cancer cell proliferation *in vitro*, and the growth of human tumor cell xenografts in nude mice [1]. The ability of E2 to modulate gene transcription is well-documented, although additional biological activities such as cytoplasmic signaling have recently been described [1].

E2 exerts its biological responses by binding to two estrogen receptor (ER) subtypes, ERα and ERβ. For many years the presence of immunopositive ERα, alone or with expression of the E2-stimulated progesterone receptor (PR), was used as a criterion for treatment of patients with adjuvant antiestrogen therapy such as tamoxifen (TAM) or ICI 182,780 (fulvestrant/faslodex) [2–5], or recently, aromatase inhibitors that prevent E2 biosynthesis [6]. ERα is present in 40–70% of breast tumors; with ER+/PR+ tumors accounting for approximately 30–50% and ER+/PR− representing approximately 10–20% of all breast tumors [2–4]. Although data on aromatase inhibitor therapy is still accumulating, only 40–80% of patients with ERα-positive (ER+) tumors respond to adjuvant antiestrogen treatment with longer time to recurrence (disease-free survival (DFS) or relapse-free survival (RFS) time), and the majority of patients eventually acquire resistance to such therapies [7,8]. Consequently, additional markers to predict clinical responses are still needed and sought. The absence of PR has been one predictor for poor responses to TAM [7,8]. Because the PR gene is ER-regulated, its expression has been interpreted to indicate a functioning ER and, therefore, an E2-responsive tumor. Alternative growth factor-sensitive pathways, identified by the presence of the EGF receptor family member HER2, are also associated with poor response to endocrine therapy and may cause decreased PR expression [8–10]. The discovery in the mid-1990s that there are two subtypes of ER, with different expression profiles in normal and malignant tissues, opened the door to the possibility that ER+ breast tumors might be even more heterogeneous than originally supposed [1]. The first ER identified and the first to determine breast tumor ER status was named ERα, and the more recently isolated receptor named ERβ. As tools to identify and measure ERβ have become available, its potential role in breast tumor formation and response to endocrine therapy is of considerable interest and investigation, and is the focus of this review.

2. Structure of ERα and ERβ

Both ERα (595 aa) and ERβ (530 aa) are members of the nuclear receptor superfamily. Although they are encoded by separate genes on different chromosomes, they have similar modular protein structures with considerable homology (Fig. 1). The DNA-binding (DBD) regions have 96% homology and bind

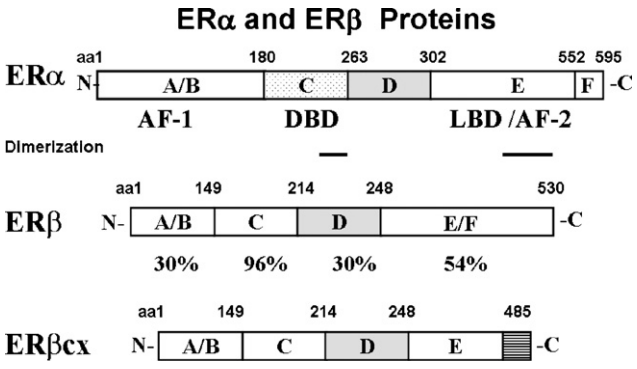

Fig. 1 – Structures of the two ER subtype proteins, and the ERβ variant ERβcx. The amino acid positions for each structural motif are shown above the proteins, and the percent amino acid homology between the two subtypes is shown below ERβ. ERβcx has 100% homology with ERβ, except for replacement of the last 61 amino acids by 26 novel amino acids, shown by the striped bar.