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The role of estrogen receptor β (ERβ) in malignant diseases—A new potential target for antiproliferative drugs in prevention and treatment of cancer

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ABSTRACT

The discovery of ERβ in the middle of the 1990s represents a paradigm shift in our understanding of estrogen signaling. It has turned out that estrogen action is not mediated by one receptor, ERα, but by two balancing factors, ERα and ERβ, which are often antagonistic to one another. Excitingly, ERβ has been shown to be widespread in the body and to be involved in a multitude of physiological and pathophysiological events. This has led to a strong interest of the pharmaceutical industry to target ERβ by drugs against various diseases. In this review, focus is on the role of ERβ in malignant diseases where the anti proliferative activity of ERβ gives hope of new therapeutic approaches.

1. Introduction

Cancers of the breast [1], prostate [2], and colon [3] are well known to involve estrogen signaling. More recently, reports have appeared that there are major sex differences in cancers of the stomach [4] and chronic lymphocytic leukemia (CLL) [5]. This review will focus on the roles of ERβ in regulating cellular growth and its loss in cancers.

If we examine the changes which have occurred in our knowledge of estrogen signaling over the past 10 years, we will see that much has happened since (and perhaps because of) our discovery of estrogen receptor beta [6].

We now know:

(1) That estrogen receptors do not only act through estrogen response elements (EREs) on DNA. They can also bind to and alter function of important signaling molecules such as AP-1, SP1, and NFκB [7]. Furthermore, different ligands can have opposing actions on these pathways depending upon whether the estrogen receptor present is ERα or ERβ.
(2) That the splice variant of ERβ, ERβcx, is abundantly expressed in certain cancers [8], and that (except for the fact that it does not bind estrogen and is a dominant repressor of ERα), its function is unknown.
(3) That the promoter of ERβ is often methylated in cancer resulting in loss of ERβ expression [9].
(4) That pharmaceutical companies have synthesized highly selective ligands for each estrogen receptor and these are in preclinical and clinical trials for the treatment of several diseases [10–16].
(5) That the ratio of ERα/ERβ in any given cell is one of the major determinants of the response of that cell to estrogen [17].
(6) That the ability of either estrogen receptor to mediate repressive or stimulatory actions on any gene is determined by the pattern of co activator and co repressor proteins in a cell [17].

In order to accommodate all of these new ideas about estrogen signaling, a new term, SERM, was coined [18]. A SERM is a selective estrogen receptor modulator. "Selective" in recognizing that there are two estrogen receptors and "modulator" in recognizing that a ligand can be either an agonist or an antagonist depending on cellular context. With this modern terminology, tamoxifen, the estrogen receptor ligand most widely used in the treatment of breast cancer, is a SERM.

Although tamoxifen is a very effective drug, two powerful drawbacks are associated with its use: (1) not all ERα-positive cancers respond to tamoxifen; (2) most patients develop resistance to tamoxifen upon prolonged use and some cancers become dependent on tamoxifen for growth. In view of our recent understanding of estrogen signaling, these negative aspects of tamoxifen can be understood and better methods for testing of cancers for (1)

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sensitivity to tamoxifen and (2) for development of tamoxifen resistance may be developed.

Even though tamoxifen is effective for treatment of most ERα-positive breast cancers [19], it is not used in prostate cancers nor is it useful for treatment of CLL. The rest of this review will discuss the role of estrogen signaling in these malignancies and the reason for their differential sensitivity to SERMS as well as the feasibility of using newer SERMs for their treatment.

2. Opposing actions between ERα and ERβ

Estrogen via ERα elicits proliferation in the breast, uterus, and developing prostate [20–22] while estrogen via ERβ inhibits proliferation and promotes differentiation in the prostate, mammary gland, colon, lung, and in stem cells in the bone marrow [23–27].

3. Is ERβ signaling aberrant in prostate cancer?

Over the past years we have examined hundreds of prostate cancer samples from many clinical collaborators. We found that ERβ is maintained in prostate cancers up to Gleason grade 3. All prostate cancers of higher Gleason scores are ERβ-negative. At present men with Gleason grade 3 are treated with watchful waiting. Since at this stage ERβ is still expressed in prostate cancer, we are advocating the use of ERβ agonists in these men in the hope that further advance in the tumor grade will be prevented by activation of ERβ.

ERβ is expressed in normal prostatic ducts in basal cells while androgen receptor is expressed in luminal cells. In prostate cancer ERβ is lost but AR remains in the luminal cells. We also found that one of the genes which were most overexpressed in ERβ−/− mouse prostate, a protease inhibitor, SPINK3, is also overexpressed in prostate cancer. The protein is called TATI and at the time of its discovery as an ERβ regulated gene, it was found by another laboratory to be overexpressed in prostate cancers [28]. We found that its expression was inversely correlated with ERβ expression in human prostate cancer. This similarity between gene expression in the ERβ−/− mouse prostate and human prostate cancer, provided some reassurance to us that gene regulation in the mouse prostate can be a useful indicator of gene expression in the human prostate. The question of the relevance of studies in the mouse ventral prostate to human prostate is often raised because of the anatomical differences between the organs in the two species.

4. Role of estrogen receptors in breast cancer

4.1. Relationship between ERs, hormone replacement therapy (HRT) and proliferation in the normal postmenopausal breast

Most human breast cancers are initially estrogen-dependent and they undergo regression when deprived of the supporting hormone. The presence of significant amounts of ERα in breast cancer at the time of diagnosis is generally taken as an indication of hormone dependence (reviewed in [17]), and, on this basis, treatment with anti-estrogen, tamoxifen, is the first-line alternative for adjuvant therapy [17]. However, ERα status is not a perfect marker for responsiveness to anti-estrogens: only 70% of ERα-positive cases respond and 10% of ERα-negative cases also respond to tamoxifen. Clearly, assay of additional and/or complementary factors is necessary to more accurately define the patients who will benefit from hormone therapy. One of the most obvious deficiencies in our knowledge about breast cancer is that we do not understand the normal postmenopausal breast. Many questions remain unanswered about what happens in the normal breast in the perimenopausal period. One of the characteristics of breast cancer in postmenopausal women is a high expression of ERα. This is seen in the cancer as well as in the normal ducts surrounding the cancer and has been interpreted to indicate a normal elevation of ERα in the absence of its ligand, estradiol.

In collaboration with Professor Britth-Marie Landgren at OBGYN, Karolinska University Hospital Huddinge, Karolinska Institutet, we have obtained 60 core biopsies from normal postmenopausal women to investigate expression patterns of ER after menopause and upon HRT. We were very surprised to find that ERα expression in normal postmenopausal breast is not elevated, indicating that the surrounding breast tissue in breast cancer samples is not normal. ERβ was expressed in more than 60% of breast epithelial cells in all but two women. In these two women ERβ was not detected but the splice variant ERβcx was very abundant. We will continue these studies to pursue the question of whether loss of ERβ is an early sign of pre-malignant changes.

4.2. ERβ agonists in the treatment of cancer

We have used two *in vivo* mouse cancer models to study the usefulness of ERβ agonists in cancer (1) xenographs in immune compromised mice and (2) dimethylbenzanthracene (DMBA)-induced breast tumors in rats. In the xenograph model we have shown that ERβ arrests tumor growth [29]. The DMBA rat model showed that ERβ is lost early in these mammary tumors. Tamoxifen acting as an ERα antagonist was effective in causing regression of these tumors but ERβ agonists were less effective. Thus it became clear that ERβ agonists would not be effective in ERβ-negative tumors. Of the four ERβ agonists (BAGs) tested, two agonists named "BAG 1" and "BAG 2" caused growth arrest and shrinkage of the tumors, while two others, "BAG 3" and "BAG 11", were ineffective. Upon microscopic examination of the regressed tumors, we noted that the major effect of the effective BAGs was to activate natural killer cells within the tumor. These cells secreted tumor necrosis factor (TNFα) and destroyed the tumor. The NK cells were the cells in the tumor expressing ERβ. This indicates that the target of cancer treatment need not be the cancer cells themselves but could rather be the immune system of the host and or patient.

These studies led us to three novel lines of study: (1) the reason for the loss of ERβ in cancer; (2) the possible use of ERβ agonists to activate immune surveillance in cancer; (3) the reason for the effects of certain but not all BAGs on the immune system.

4.3. Reason for loss of ERβ in cancer

The reason for the loss of ERβ in cancer appears to be due to silencing of the ERβ by promoter methylation [30]. The CpG islands in the ERβ promoter are methylated and transcription of the gene is suppressed. This finding suggests a novel strategy for treatment of or prevention of the progression of cancers, i.e., prevention or reversal of the silencing of ERβ.

Recent studies by Stettner et al. [31] show that demethylation of the ERβ promoter by valproic acid is possible and when this is done in prostate cancer cell lines, the cells re-express ERβ. Up-regulation of ERβ resulted in antiproliferative effects. Thus, these drugs, by restoring the regulatory function of ERβ in tumor cells, could become useful in the intervention of cancer.

4.4. Role of ERβ in immune surveillance in cancer

Both ERα and ERβ are found in hematopoietic cells in bone marrow and in B lymphocyte precursors in mice. ERβ has also been found in human spleen [32]. Estrogen has contradictory effects in autoimmune diseases. Although it appears to offer protection against end-stage renal disease, during the development of systemic lupus erythematosus (SLE), estrogen blocks the destruction

of immature auto-reactive B cells in the bone marrow of mice and promotes autoimmunity [33]. Thus, estrogen relieves the symptoms of T cell dominant autoimmunities, rheumatoid arthritis (RA) and Sjogren's syndrome (SS), but it exacerbates B cell dominant ones, like SLE. These contradictory effects of estrogen on autoimmunities are not well understood.

One target of ERβ in cancer is immune surveillance. Recently, a role for estrogen in the ability of tumors to block immunosurveillance was suggested by Shapiro. In breast cancer cells, estrogen and tamoxifen via ERα induce expression of the SerpinB9/proteinase inhibitor 9 (PI-9) and progressively blocks cell death induced by NK92 natural killer (NK) cells [34]. NK cells are part of the innate immune system and play a critical role in tumor immune surveillance. It would clearly be of clinical value if novel therapies that increase T-cell trafficking into tumor nests are developed. We have found that while ERβ is expressed in circulating and passenger lymphocytes in normal tissues and in breast and prostate cancer, the immune cells within tumors do not express ERβ.

4.5. ERβcx in estrogen signaling

One major difference in ERβ signaling between rodents and humans is the difference in the predominant splice variant of ERβ expressed in the two species. Humans but not rodents express the splice variant, ERβcx. ERβcx [35] is identical to ERβ (now designated ERβ1) except that the last 61 C-terminal amino acids have been replaced by 26 unique amino acid residues. Expression of ERβcx is higher than that of ERβ1 in some breast [8,36] and prostate [37] cancers. At present, the clinical significance of ERβcx is under intensive investigation. ERβcx does not bind estradiol and has no capacity to activate transcription of estrogen-sensitive reporter genes. ERβcx heterodimerizes preferentially with ERα and this has a dominant negative effect on ligand-dependent ERα reporter-gene transactivation. Since ERβcx inhibits DNA binding of ERα, ERβcx might render ERα non-functional in estrogen-dependent tissues. The effect of ERβcx expression on the outcome of breast cancer is a hotly debated issue and no clear answers have yet emerged. The most important message to oncologists is that it is not sufficient to measure ERβ in cancers. It is necessary to use antibodies that distinguish between ERβ and ERβcx.

5. Tissue specific effects of BAGs (ERβ agonists): co regulators in ERβ function

Upon ligand binding, the nuclear receptors (NRs) change conformation, hiding some regions and exposing others, resulting in dissociation of co-repressors, dimerization, recruitment of co-activators, and binding to promoter regions of different responsive genes (recently reviewed in [17]). The combination of co-factors recruited to the ERs is of major importance in determining the distinct pattern of effects evoked by different stimuli in different cell types and at different points of tissue maturation. In the case of ERs, different ligands result in different conformations of ER thus modulating the affinity for co-factors. Although they bind to the same response elements, the two ER isoforms have quite different (sometimes opposing) effects in different tissues. Identification of tissue and cell-specific ER complexes requires isolation of these complexes. So far efforts in other labs to isolate nuclear receptor complexes have been limited to one cell type made to overexpress an epitope-tagged nuclear receptor or co-regulator using subsequent laborious fractionations, pull-downs and/or immunoprecipitations using antibodies against the epitope tags. Identification of estrogen receptor protein complexes is a daunting task: the more purification steps one includes, the more material is lost, including some proteins which are more loosely bound but none the less important components of the complex. We have recently managed to isolate a large number of proteins which specifically bind to ERα, using an ERE-based affinity matrix and MCF-7 breast cancer cells [38]. Characterization of the potential role of these proteins in estrogen signaling is currently ongoing in our laboratory.

6. Estrogen receptors in the immune system: involvement in the pathogenesis of CLL

The importance of estrogen and the ERs in the immune system has been studied using three different animal models: ERα−/−, ERβ−/−, and the aromatase knockout (Ar−/−) mice. Loss of each component in the estrogen signaling pathway produced a distinct immune phenotype with development of autoimmune nephritis in ERα−/− mice [39], myeloid leukemia in ERβ−/− mice [27] and Sjogren's syndrome in Ar−/− mice [40]. These results indicate a novel role for ERs in regulating the differentiation of pluripotent hematopoietic progenitor cells. Autoimmune diseases affect women primarily, with some occurring 10 times more frequently in women than in men [41]. Estrogen has contradictory effects in autoimmune diseases. The different effects of estrogen may be mediated by its interactions with ERα and ERβ. A previous study showing the development of autoimmune glomerulonephritis in ERα−/− mice (cf. above) suggests that an imbalance between ERα and ERβ is important for the development of autoimmunity.

B cell CLL is characterized by the accumulation of a clone of malignant B cells in lymphoid tissues, bone marrow and peripheral blood [42]. Progressive CLL is frequently associated with autoimmune complications including autoimmune hemolytic anemia and thrombocytopenia [43]. The mechanism of autoimmunity may be related to the imbalance of T cell subsets. ERβ is the predominant ER in mature lymphocytes in healthy individuals [32]. Recently, we have analyzed the expression of ERα, ERβ, and ERβcx in total peripheral blood mononuclear cells (PBMC) from CLL patients and healthy donors. As discussed above, ERβcx is a splice variant of ERβ which is a dominant repressor of ERα signaling. Although the physiological function of ERβcx is unknown, its presence in cells together with ERα and ERβ should alter the balance between ERα and ERβ. Our preliminary results show that expression of ERβcx in total PBMCs from CLL patients is higher than in PBMCs of healthy individuals. An intriguing question is whether estrogen receptors in B cell CLL may be used as a new target in the treatment of this disease.

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