Molecular and Physiological Roles of Estrogen Receptor

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Abstract

Estrogen receptor (ER) has been shown to be involved in several cellular and metabolic pathways. In this study, we reviewed the literature for molecular and physiological roles of estrogen receptor in normal and pathological conditions. We discussed the expression of estrogen receptor in several tissues as well as the potential of using ERb agonists in treating proliferative hematological disorders. The function of estrogen is varied and may look contradictory. Estrogen has multiple roles under physiological conditions including signaling roles in cell growth, reproduction, development and differentiation. Estrogens exert their effects through two distinct estrogen receptors, ER-α and β to which E2 binds strongly. The expression of ERs depends mainly on the type of ER. Although estrogen mainly acts in reproductive system, its receptors are selectively expressed in different tissues. ER-β is highly expressed in the ovary, central nervous system, cardiovascular system, lung, male reproductive organs, prostate, colon, kidney and the immune system. ERb is highly expressed in lymphoid cells, and the finding of anti-proliferative roles of ERb, the potential to use ERb agonists in treating proliferative hematological disorders has been raised. Taken together, the function of estrogen seems to be determined by the estrogen receptor which is expressed in various tissues with relatively predominant forms. There is a potential to used ERb agonists in treating proliferative hematological disorders.

Keywords: Estrogen receptor; Molecular; Physiological roles

Introduction

Due to the importance of estrogen and its receptor, estrogen receptor (ER), we conducted this review study to bring to the reader a good source of information. In general, we may thought that ER is being of main interest in reproductive system. As will be seen in the following sections, estrogen and ER have vital roles in multiple pathways from normal physiological conditions to inflammatory conditions and carcinogenesis. This review discusses the role of ER as a signaling molecule, its variants, its role in proliferation and apoptosis, its role in immunity, its role in inflammation, autoimmunity, tumors, and its therapeutic role in treating cancer.

Signaling pathways of ER

Estrogens are included in regulating various physiological processes such as cell growth, reproduction, development and differentiation. Estrogen is mainly synthesized in premenopausal women by ovaries as 17b-estradiol (E2) which, in turn, exerts its effects on target organs and cells. On the other hand, the main source of E2 in postmenopausal women and in men comes from the conversion of extragonadal sites of testosterone and androstenedione into E2 by the action of cytochrome P450 aromatase enzyme[1]. However, E2 has significant roles in mediating various pathological processes such as carcinogenesis[2]. Furthermore, estrogens exert their effects through two distinct estrogen receptors, ER-α and β to which E2 binds strongly[3].

ERs can bind through three binding sites or domains: one is called NH2- terminal domain, another one binds the DNA, and the third one binds the ligand domain[4]. According to[3], there is a ligand-independent activation function (AF1) re-
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Expression of the ERs and their splice variants

The expression of ERs depends mainly on the type of ER. The expression of ER α is shown particularly in reproductive system (uterus, ovary), breast, kidney, bone, white adipose tissue and liver. On the other hand, ER-β is highly expressed in the ovary, central nervous system, cardiovascular system, lung, male reproductive organs, prostate, colon, kidney and the immune system[19,20]. Numerous studies have pointed to the expression of various isoforms of both ER-α and ER-β, which are derived from alternative splices. Such splice variants have been detected in a wide range of cells from normal cells to cancer cell lines and samples from different types of cancer[15]. In this context, several studies have demonstrated ER-α mRNA splice variants in cell lines and samples from breast, endometrial, ovarian and colorectal[23-28]. ER-β has some variants that were detected in various tumors such as breast cancer[27], endometrial cancer[28,30] and thyroid cancer[31]. According to[22], wild-type ERs, splice variants of ER-α and ER-β were shown to be expressed in normal lymphoid cells. It is worth to mention that ER-α is localized in the nucleus and the cytoplasmic membrane of breast cancer cells, and it is thought that this leads to rapid signals resulting in cell proliferation and survival upon ligand binding[31]. Other researchers have pointed to the membrane expression of ER-β[34,35].

Other studies are still required to correlate the expression of ER with other proteins including Bcl2, p53, and possibly others because of possible shared roles that may interact with the expression of ER.

ER-mediated effects on proliferation and apoptosis

ERs induce opposed effects on proliferation and apoptosis. Estrogens have been shown to increase the growth of the breast, uterus, and prostate, which implies the possibility to induce carcinogenesis[36-40]. Other studies employing ER-β knock-out mice revealed contradicting findings in which estrogens through ER-β repress proliferation and induce differentiating stem cells in various tissues[39,40,41-44].

According to[41], findings derived from ER-β knock-out mice showed prostate hyperplasia and a myeloproliferative disease which were similar to human chronic myeloid leukemia. Transfection studies involving breast and colon cancer cells that are deficient in ER-β revealed that the addition of ER-β results in reduced cell proliferation either in culture or in vivo in xenograft studies[45-49]. ER-β has been found in transfection studies to suppress cell proliferation in a hormone-independent way, which leads to the conclusion that ER-β may act as a tumor suppressor[45,47,48]. Various studies that target the effects of E2 on apoptosis revealed conflicting results. Some studies have pointed to inhibitory effects of E2 on growth of cells in lymphoma cells by activating apoptotic pathways[50,51]. Another study by[52] pointed to the enhanced apoptosis in osteoclasts by E2. Other studies showed contradicting findings. As an example, it has been reported that E2 has an anti-apoptotic action on T-lymphocytes and monocytes in vitro. Furthermore, it can inhibit apoptosis in cardiomyocytes in vivo[3,53]. Other researchers showed that E2 can control apoptosis pathways in cancer cells as well as normal cells[54,55]. E2 up-regulates Bcl-2 gene in ovarian epithelial cells[56].

Other studies revealed that binding of E2 to ER-β can induce apoptosis[56]. Furthermore, ER-β up-regulates Fas-L in epithelial cells of ovary[57]. Other studies reported the induction of apoptosis of ER-β in prostate and ovarian cancer cells[56,57,58]. In a vitro study employing epithelial cell lines showed that E2 promoted cell survival through non-genomic signaling of ER-α and cell death through non-genomic signaling of ER-β[59].

According to[60], when murine lymphoma cell lines were exposed to ER-β agonist, apoptosis was more likely to be induced. Taken together, the previous context showed that ER-β has, in general, a pro-apoptotic effect, while ER-α has an anti-apoptotic effect. Furthermore, the responses depend on and to larger extent correlates with the expression of ER subtype. The existing literature does not give clear answers when the ER is likely to induce apoptosis or proliferation which opens the door for more studies. We think that future studies may point out to more diagnostic and therapeutic options which may depend on the individual context.

Expression of ERs in immune cells and their functional role

Effects of ERs in lymphocytes: Several studies have emphasized the detection of the mRNAs and proteins of ER-α and ER-β in PBMCs and neutrophils[52,53]. It has also been re-
ported that subcellular differences also exist, and CD4+ T cells express elevated concentrations of ER-α mRNA whereas B cells express largely ER-β mRNA[60]. Concerning protein levels[61], reported that ER-β is the dominant ER expressed in mature leukocytes from peripheral blood, tonsils or spleen of healthy individuals. Taking into consideration that B cells are expressing more ER-β mRNA compared to ER-α mRNA, it has been found that various cell lines of lymphoma that give examples for lymphomas including Hodgkin lymphoma to greatly over express the proteins of ER-β, whereas the proteins of ER-α is either expressed in low levels or even not detectable[64,66]. In another study by[64], both ER-α and ER-β proteins were expressed in NK cells.

Effects of E2 on lymphoid cells: Estrogens have significant effects on the innate and the adaptive immune system[65]. Other studies showed the effect of estrogens on thymus and bone marrow[66-68]. Furthermore, it has been found that estrogens have a suppressive effect on both B and T lymphopoiesis. As an example, the formation of B lymphocyte selectively lowers the bone marrow of mice treated with E2[69], while other studies showed that ovariectomy of mice increased B lymphopoiesis[69,70]. Another study showed that E2 can impair the maturity of B cell maturation[71]. Other studies examining the effects of treatment with E2 on T cell populations revealed thymic involution with reduction of T lymphopoiesis[68,69,72]. Other studies depended on treatment using ER-α-selective agonist PPT showed thymic atrophy as well as important variations in the proportion of CD4/CD8 in thymus which implies that ER-α can play a principal role in atrophy of thymus induced by estrogen[73]. According to a study by[74], treatment with E2 prevented T cell-dependent immune reactions, whereas there was an improved antibody production from B cells[75]. It has been explained that how the effect of treatment with E2 is mediated on T cell immune responses by a study of[76] who proposed a mechanistic explanation in which the expression of ER-α was detected in CD4 + CD25T cells and introducing physiological doses of E2 was able to increase the expression of Foxp3 in vitro and converted T cells from the CD4 + CD25phenotype into regulatory CD4 + CD25 + T cells.

ERS and E2 in myeloid cells: Various studies showed the expression of ER-α and ER-β in some myeloid cells including monocytes, macrophages and dendritic cells (DC)[77-80]. The expression of ER-β has been shown to predominate in Monocytes, whereas ER-α is more expressed in macrophages[78]. The functions of estrogens are varied in cells of the myeloid cell lineage that include maturation, differentiation and migration[80]. Moreover[81], indicated that E2 has certain effects on innate immune reactivity such as improved phagocytic capacity in neutrophils and phagocytes. Within this context[82], expressed their views in explaining the large variation seen in innate immune reactivity among men and women.

Other studies have indicated that E2 can stimulate the differentiation of DCs from bone marrow DC[83,84]. It is worth to mention that E2 can improve the role of presentation of antigens of DCs through over expressing MHCII[83,85]. The differentiation of DCs is prevented in ER-α knock-out bone marrow cells which points to a predominant role for ER-α in this process[85]. Another study has further demonstrated the need for ER-α in the production of a Toll-like receptor of IFNa by plasmacytoid DCs[87]. Taking into account the previous studies, it seems that estrogens and their receptors are

ERs and estrogens in inflammation

It is well-known that the response to inflammation is a major function of the immune system[81]. This function is under the effect of E2 because E2 has inducing influences on immune system which explains why women are more resistant to infections compared with men[83]. Under inflammatory conditions, studies pointed to up-regulation of ER-β and down-regulation of ER-α in splenocytes. This phenomenon is further confirmed under hypoxic conditions in which immune and endothelial cells are accompanying inflammation and as a result, ER-β is up-regulated while the expression of ER-α is down-regulated[85].

Previous studies have shown that E2 has effects on pro-inflammatory transcription factors and cytokines. Furthermore, the activation of immune cells resulting from either microbial origin or signals induced by inflammation is controlled by stimulation of the nuclear factor-kappa B (NF-κB), the required pathway for the normal responses by immune cells[86]. In another study, researchers have shown that both ER-α and ER-β prevent the activity of NF-κB based on E2 in cardiac myocytes in vitro[89]. Furthermore, a selective ER-β agonist ERB-041 inhibits the activity of NFκB in peritoneal macrophages[89]. Taken together, both ERs inhibit NFκB activity in different cell types. Several studies have put emphasis that the expression of adhesion molecules to be regulated by E2 and the outcomes are dependent on the concentration of E2. These studies denoted that E2 levels at pregnancy suppress the expression of membrane E-selectin, and intercellular adhesion molecule-1[91,92]. Low levels of E2 up-regulate the expression of the adhesion molecules[85]. E2 can regulate expression of both pro-inflammatory and anti-inflammatory cytokines. E2 has various effects on the formation of reactive oxygen species (ROS) that so increased levels of E2 lower the formation of ROS, while either ovariectomy or low levels of E2 increase the production of ROS[85].

The effects of E2 on the expression of inflammatory (NO) synthase (iNOS) have been reported. Elevated levels of E2 have been shown to inhibit NO production stimulated by cytokine[93]. Another study pointed to the involvement of ER-α in the inflammation of vascular tissues which is associated with diabetes indicating that E2 decreases the level of (iNOS) in the aorta via ER-α[86]. The relationship between chronic inflammatory diseases and development of fibrosis has been established[94]. Other studies showed that E2 has effects on functions of fibroblasts and mechanisms of fibrosis. According to[95], E2 up-regulates basic fibroblast growth factor and the tissue inhibitor of MMPs (TIMP)[97]. Another study found that E2 could suppress a hepatic fibrosis[96,99]. Proposed an explanation of suppressed fibrosis by E2 in which hepatic stellate cells express ER-β, but not ER-α. Moreover, E2 has the ability to inhibit the fibrosis of heart through ERb in vivo[95]. High levels of estrogens can inhibit inflammation through making a reduction in pro-inflammatory pathways[85]. It is worth mentioning that ER subtype that is expressed in individual cell determines how the response to E2 will be by inflammatory cells.

The roles of ERs in autoimmunity

Estrogens have been shown to be one of the risk factors of autoimmunity; women are more likely to be affected by au-
to autoimmune diseases during the stages of fertility compared with men. It is greatly considered that both B and T lymphocytes to be crucial in the initiation of autoimmune diseases\(^{69}\). E2 has its influences on lymphoid and myeloid cells which can be mediated through the expression of ERα and ERβ. Various trials were made to demonstrate the roles of estrogens and ERs in autoimmune diseases. One of these trials was made in murine lupus models indicated that early removal of ovary of NZB/NZW f1 mice was able to reduce the progression of lupus. It has been shown through two studies that breeding of the ERα/ genotype with three different murine lupus-prone strains provided protection against renal pathology by lacking ERα\(^{100,101}\). Also, a study showed that E2 has the ability to lower the tolerance of B-cell by ERα\(^{71}\).

In another study by\(^{44}\), the results showed that the deficiency of ERα led to the development of autoimmunity, whereas the use of ERα agonist PPT has therapeutic effects on some autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. In their study\(^{102}\), showed that the removal of ovary has impacts on lupus progression which were reversed by treating with E2. The results also showed that the use of E2 or the ERα selective agonist was able to ameliorate the clinical output of arthritis compared to control group. It seems that these studies did not link the role of estrogens with infectious diseases together to participate to autoimmune diseases. Here, we would like to recommend future diseases to focus in this point because solving the estrogen problem would be an interesting area to help in autoimmune remedies.

### The roles of ERs in lymphoid tumors

According to\(^{15}\), numerous tumors exhibit their E2 dependency including endometrial and breast cancers. Irrespective to the fact that hematological malignancies do not depend on hormones to be initiated, it seems that lymphoid malignancies tend to be under the effect of estrogen as indicated by epidemiological studies which pointed to gender variations regarding incidence and prognosis\(^{43,103,104}\). Other studies pointed to the existence of an association between reproductive hormones and oral contraceptives with lowered risk factor among female patients with Non-Hodgkin lymphomas\(^{48,106}\). In general terms, studies showed that men are more likely to develop acute lymphocytic leukemia\(^{41,105}\) and CLL\(^{100}\) compared with women. Other studies showed a higher incidence of lymphoid neoplasm subtypes in males compared with females, among these examples are Burkitt lymphoma and mantle cell lymphoma, whereas in T-cell neoplasms, no significant differences were reported among females and males\(^{45}\).

In the study of\(^{61}\), the authors reported an evidence to show the effect of E2 on growth of lymphoma so that the mice grafted with T cell lymphoma cells, the tumor size was greater in males compared with females. The expression of ERβ has been reported in both Burkitt’s lymphoma cell lines\(^{41}\) and PBMCs from CLL patients\(^{61}\). Actually, it can be implied from such findings that the agonist of ERβ can influence lymphoma and leukemia cells. It is believed that the consideration that wild-type ERβ is expressed in lymphoid tumors as well as ERβ2 in CLL patients\(^{61}\). From a clinical point of view, the expression of ERβ2 may indicate poor prognosis. In another study by\(^{31}\), it was found that the expression of ERβ2 was able to increase the growth of cancer cells in prostate using mice model. The expression of ERβ2 has been reported in low levels in mammary glands at physiological conditions, whereas its expressed levels have been significantly increased in invasive mammary carcinomas\(^{105}\). The localization of ERβ2 as either only in cytoplasm, or both cytoplasmic and nuclear plays a crucial role in evaluating the prognosis so that the involvement of cytoplasmic localization implies poor prognosis\(^{106}\).

In their study\(^{107}\), pointed to a very interesting finding when the ERβ were found localized in membranes. The authors expressed their thoughts as ERβs have a role in differentiation of hematopoietic cells. In a previous study, ERβ knockout mice developed myeloproliferative disease, lymphoid proliferation, and prostate hyperplasia\(^{44}\). It can be extracted from these findings that ERβ has a potential to inhibit the growth of myeloid cells and accordingly it can be considered as a tumor suppressor in hematological malignancies. The role of estrogens in lymphoid tumors looks to be independent from gender which highlights the need for future research to address the molecular aspects associated with estrogen.

### The therapeutic potential of ERβ agonists in treating cancers

Based on previous findings in which ERβ is highly expressed in lymphoid cells, and the finding of anti-proliferative roles of ERβ pointed to the possibility of using ERβ agonists in treating proliferative hematological disorders. Several ERβ selective agonists have been produced but not seriously tested against hematological tumors\(^{61,108}\). It was interestingly to find that no cross reactivity is found between ERβ and ERα\(^{61}\). The application of ERβ agonist did not exhibit any impacts on the growth of lymphoma\(^{61}\). It can be extracted from these findings that ERβ agonists can be used as a therapy for lymphomas expressing ERβ.

Other studies showed that some natural compounds may prefer ERβ which may makes a new line of therapeutics for hematological tumors. As an example, genistein, has affinity for ERβ can arrest G2/M cycle and increase the differentiation of acute myeloid leukemia cells\(^{109}\). It can induce apoptosis in T-cell leukemia cells\(^{100}\), it can also prevent the growth of canine lymphoid cell lines\(^{111}\). The study of\(^{12}\) showed that the improved expression of ERβ in cell lines of breast cancer arrested a G2 cell cycle. In another study by\(^{112}\), it was found that the ERβ agonist DPN exhibited antigrowth impacts on breast cancer cells. Other studies have demonstrated the expression of ERβ in prostate cells either normal or malignant cells, or accordingly, it is plausible to use ERβ agonists in treating prostate malignancies. There is evidence from in vitro studies showing that treatment of prostate cancer cell lines with ERβ was able to lower growth, invasiveness, and induced apoptosis in these cells\(^{36,37,113}\).

Other studies showed that the use of ERβ agonist DPN decreased the potential of tumorigenesis of intestine using ApoC(Min/+)(Mice\(^{114}\)). Another study reported that DPN was able to prevent colon cancer cells expressing ERβ\(^{115}\), whereas medulloblastoma cells were inhibited from growth in vivo using a mouse model\(^{116}\). In another study, the ERβ agonist KB9520 showed antitumorogenic impacts using rat models of cholangiocarcinoma\(^{117}\). Although the previous studies showed the potential of using ERβ agonist in treating cancers, there is still a need for more studies to explore more mechanisms of action and to specify the exact pathways for optimal use of this promising line of cancer therapy.
Discussion

The present study reviewed the literature for the estrogen and ERs. Estrogen has multiple roles under physiological conditions including signaling roles in cell growth, reproduction, development and differentiation. Estrogens exert their effects through two distinct estrogen receptors, ER-α and β to which E2 binds strongly[39]. It seems that it is difficult to put the actions or roles of estrogens and ERs in one frame. There is a need in future research to identify the conditions in which the estrogens behave and what are the stimulating factors.

The expression of ERs depends mainly on the type of ER. Although estrogen mainly acts in reproductive system, its receptors are selectively expressed in different tissues. ER-β is highly expressed in the ovary, central nervous system, cardiovascular system, lung, male reproductive organs, prostate, colon, kidney and the immune system[21,22]. A debate concerning the roles of estrogen has been discussed and ended with contradicting findings in which it was thought that it increases the proliferation and growth to increase the growth of the breast, uterus, and prostate, which implies the possibility to induce carcinogenesis[38-40]. On the other hand, other contradicting findings showed that Other contradicting findings showed that estrogens through ER-β repress proliferation and induce differentiating stem cells in various tissues[39,40-44].

According to the context that ER-β is highly expressed in lymphoid cells, and the finding of anti-proliferative roles of ERβ, the potential to use ERβ agonists in treating proliferative hematological disorders has been raised[112,114,115,117]. Estrogens through its receptors interact with the nucleus material in the cell and activate other genes such as BCL2 gene which, in turn, induces the production of BCL2 protein in cytoplasm and makes the cell ready for division and proliferation. In this context, we may ask a large question which we do not observe in studies about the source and concentration of estrogen. If estrogen comes from other sources into the body, its concentration may become more than under control in cellular processes and it is plausible to think of extra actions of estrogens which may exceed metabolic needs and makes it involved in carcinogenesis. Accordingly, we think that a lot of further research is still required to explore the role of estrogen.

Conclusions

The function of estrogen seems to be determined by the estrogen receptor which is expressed in various tissues with relatively predominant forms. The function of estrogen is varied and may look contradicted. There is a potential to use ERβ agonists in treating proliferative hematological disorders.

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