

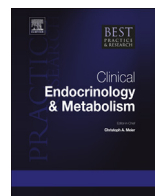


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Estrogen receptor alpha and beta in health and disease



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Estrogen receptors alpha (ER α) and beta (ER β) are transcription factors that are involved in the regulation of many complex physiological processes in humans. Abnormal ER signaling leads to development of a variety of diseases, such as cancer, metabolic and cardiovascular disease, neurodegeneration, inflammation, and osteoporosis. This review provides an overview and update on ER α and ER β in health and disease with focus on their role in cancer and metabolic disease and in the context of recent years' success in providing genome wide data on ER function. Furthermore, potential clinical applications and challenges are also discussed.

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Estrogens regulate various physiological processes such as cell growth, reproduction, development and differentiation. In premenopausal women, the ovaries are the primary site of estrogen synthesis producing the predominant estrogen 17 β -estradiol (E2), which acts locally and systemically on target organs and cells. In postmenopausal women and in men, the source of E2 is local conversion of testosterone and androstenedione to E2 by the cytochrome P450 aromatase enzyme in extragonadal

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sites, such as breast, brain and adipose tissue where it acts locally as a paracrine or intracrine factor. In addition to effects by E2 on normal cells and normal physiology, estrogens also play an important role in several pathological processes including cancer, metabolic and cardiovascular disease, neurodegeneration, inflammation, and osteoporosis. The cellular effects of estrogens are mediated by two estrogen receptors, ER α and ER β .

Estrogen receptors: expression, structure and isoforms

The existence of an ER was demonstrated by Elwood Jensen in 1958 [1], and the corresponding gene was cloned in 1985. ER β , was cloned from the rat prostate and ovary in 1996 [2]. ER α is mainly expressed in reproductive tissues (uterus, ovary), breast, kidney, bone, white adipose tissue and liver, while expression of ER β is found in the ovary, central nervous system (CNS), cardiovascular system, lung, male reproductive organs, prostate, colon, kidney and the immune system. As members of the nuclear receptor protein family, ERs are found mainly in the nucleus, but also in the cytoplasm and mitochondria.

The ER α and ER β genes are located on different chromosomes, 6q25.1 and 14q23.2, respectively. ERs are composed of three functional domains: the NH₂-terminal domain (NTD), the DNA-binding domain (DBD), and the COOH-terminal ligand-binding domain (LBD) (Fig. 1). The NTD encompasses a ligand-independent activation function (AF1) domain involved in transcriptional activation of target genes, and with only 16% similarity between ER α and ER β . The DBD is highly conserved between ER α and ER β with 97% amino acid identity and mediates sequence-specific binding of ERs to DNA sequences in target genes denoted estrogen-responsive elements (EREs). In contrast, the LBDs of ER α and ER β show a 59% overall amino acid sequence identity yet the ligand-binding pockets of the two subtypes show only minor differences in structure. Importantly, these small structural differences in the ligand binding pockets have allowed the development of subtype selective ligands. Propyl pyrazole triol (PPT) and 2, 3-bis (4-hydroxyphenyl)-propionitrile (DPN) are commonly used ER α and ER β selective agonists, respectively. The LBD also contains a ligand-dependent activation domain (AF2).

Due to alternative splicing of ER-mRNAs, three ER α isoforms have been identified (Fig. 1). ER $\alpha\Delta$ 3 lacks exon 3, which encodes part of the DNA-binding domain [3]. ER α 36 lacks both AF-1 and AF-2, and the last 138 amino acids (aa) are replaced with a unique 22 aa sequence [4]. ER α 46 lacking aa 1–173

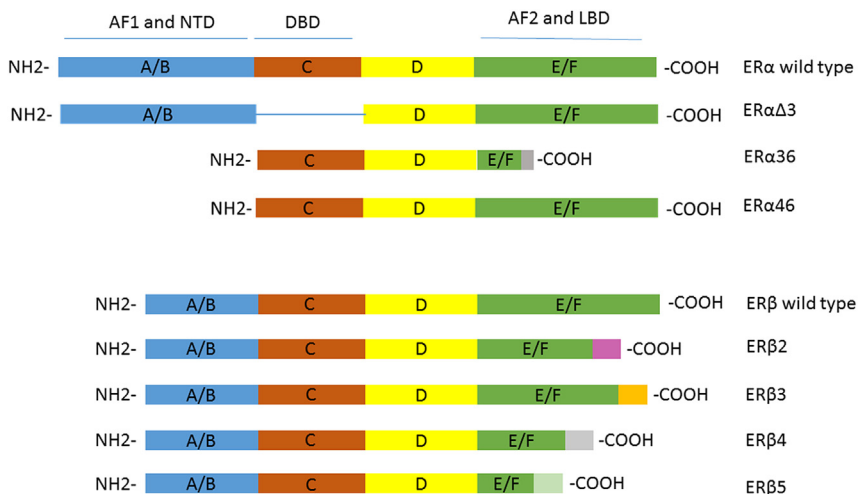


Fig. 1. The structures of the ER isoforms. Different functional domains are highlighted: the NH₂-terminal domain (NTD) in blue, DNA-binding domain (DBD) in orange, and the COOH-terminal or ligand-binding domain (LBD) in green. The NTD contains a ligand-independent activation function (AF1) region which is responsible for recruitment of co-regulatory proteins.

which includes AF-1, was first identified and characterized as a dominant negative inhibitor of ER α activity in osteoblasts [5]. For ER β , at least four ER β isoforms have been described, referred to as ER β cx/2, ER β 3, ER β 4 and ER β 5 [6] (Fig. 1). All ER β variants have novel C-terminus, and are unable to bind estrogens and other investigated ligands.

Genome-wide studies of ERs

ER cistromes

Consistent with the fact that ER α and ER β are highly homologous in their DNA-binding domains, identification of DNA binding regions showed substantial overlap in binding sites for the two ERs [7]. Both receptors interact with binding sites enriched in ERE motifs [8]. However, ER α and ER β also display differences in bound DNA regions [9]. Additionally, the binding of one receptor affected the binding pattern of the other [10]. ER cistromes may correlate with human disease and response to treatment. For example, analysis of ER α DNA binding sites demonstrated that FOXA1 is a major determinant of estrogen-ER activity and endocrine response in breast cancer cells [11].

ER transcriptomes

Gene expression profiling of ER α showed up-regulation of for example cell growth related genes [12]. Enriched functional clusters of ER β modulated genes included signal transduction pathways, and genes controlling cell cycle progression and apoptosis [13]. Analysis of ER α - and ER β -mediated gene regulation in the T47D cell line with inducible expression of ER β , revealed that ER β had diverse effects on ER α regulated gene expression, enhancing or counteracting the effects of ER α [14]. ER β inhibited approximately 70% of ER α regulated genes including genes involved in proliferation and metabolism [14]. These findings suggested that ER α and ER β in breast cancer cells likely impact cell proliferation and the activities of diverse signaling pathways.

ER interactomes

ERs regulate transcription via recruitment of different transcriptional coregulators (CoRs), which play a central role in the activation (coactivators) or repression (corepressors) of genes. Less than 50% of these CoRs were common to both ERs, suggesting that differences in interactomes of the two ERs are likely to contribute to the distinct roles of the two receptor subtypes [15]. Comparative analyses of agonist (E2) versus antagonist tamoxifen (Tam), raloxifene (Ral) or ICI 182,780 (ICI)-bound ER α interacting proteins reveal significant differences among ER ligands that relate to their biological activity. In particular, the E2-dependent nuclear ER α interactome is different and more complex than those elicited by Tam, Ral, or ICI, which, in turn, are significantly divergent from each other [16].

ERs and cancer

ERs and breast cancer

ER α and breast cancer

ER α is expressed in not more than 10% of normal breast epithelium but approximately 50–80% of breast tumors [17]. It is found in both ductal and lobular epithelial and stromal cells.

The role of ER α in mammary gland development has been demonstrated in ER α knockout (ER α KO) mice [18]. ER α promotes tumorigenesis and progression of breast cancer. Anti-hormonal therapy is commonly used in breast cancer patients with ER α expression, including the selective estrogen receptor modulators (SERMs) tamoxifen, raloxifene and toremifene, the selective estrogen receptor degradator fulvestrant, and the aromatase inhibitors anastrozole, letrozole and exemestane. Tamoxifen is the most effective and widely used antiestrogen therapy for breast cancer. However, only 70% of ER α positive breast cancers respond to tamoxifen treatment and 30–40% of patients receiving therapy relapse and become resistant to this therapy [19]. Additionally, tamoxifen, serving as an estrogen

antagonist in the breast, mimics estrogen effects acting as an estrogen agonist in other tissues, such as bone, endometrium and the cardiovascular system, thus having potentially severe side effects in these tissues. Another SERM, raloxifene, is reported to have less profound side effects compared to tamoxifen, particularly with decreased risk of endometrial cancer and thrombosis.

The ratio of ER α Δ 3 to wild type ER α is substantially reduced in all breast cancer cell lines and in breast cancers, suggesting that loss of the ER α Δ 3 isoform is associated with an early event in carcinogenesis. Molecular studies suggest that ER α Δ 3 functions as a dominant negative regulator of ER α . ER α 36 has been shown to correlate with carcinogenesis, aggressiveness, and therapeutic response of breast cancer. Binding to the same target DNA sequence as wild type ER α does, ER α 36 is expected to function as a powerful competitor of ER α . However, ER α 36 mainly locates to the plasma membrane and to the cytoplasm where it activates rapid membrane-initiated non-genomic pathways. In recent years, studies have focused on the association between ER α 36 and tamoxifen resistance [20]. Additionally, ER α 36 is highly expressed in ER α -negative breast cancer. ER α 46 acts as a negative regulator of breast cancer. Its overexpression inhibited MCF-7 breast cancer cell proliferation and inhibited E2-induction of the cyclin D1 promoter [21] and ER α regulation of pS2 gene [22]. ER α 46 levels were reduced in tamoxifen resistant breast cancer cells and ER α 46 re-expression inhibited cell proliferation [23].

ER β and breast cancer

ER β knockout (ER β KO) mice undergo an overall normal mammary gland development. However, subtle effects associated with decreased differentiation and increased proliferation in the alveoli of lactating mammary glands are sometimes observed in these mice [24]. Approximately 80% of normal breast epithelial cells express ER β . Its expression is decreasing and even lost during breast cancer progression, which is associated with promoter hypermethylation [25]. *In vitro* studies showed that re-expression of ER β in breast cancer cell lines inhibited cell proliferation, promoted apoptosis and enhanced the efficacy of chemotherapeutic agents [26]. Clinical evidence also revealed that loss of ER β expression is associated with a poor prognosis [27] and resistance to endocrine therapy [28]. ER β inhibits breast cancer cell proliferation through repressing activation of MAPK and PI3K signaling pathways [29]. Regulation of genes controlling cell cycle progression and apoptosis, may also contribute to the suppression of cell proliferation [13]. However, a few studies claim that ER β expression is associated with enhanced cell proliferation, and is a poor prognostic factor in breast cancer [30,31]. Other studies claimed that ER β expression was not correlated with clinical outcome in breast cancers in postmenopausal patients [32].

The expression and role of ER β 2 in breast cancer remain unclear [33]. Some studies showed that ER β 2 expression levels are lower in cancer compared with the corresponding normal tissues, indicating a protective role in breast cancer. Consistently, studies showed that ER β 2 is a good prognostic indicator in breast cancer. A possible mechanism may be repression of ER α activity by induction of proteasome-dependent degradation [34]. Other studies report opposite effects, and claim that ER β 2 expression is indicative of cellular proliferation [35]. Some studies showed that ER β 2 predicted the response to endocrine therapy [36] while other studies did not reproduce such effects [37].

ER β 5 exhibited protective role in breast cancer patients. Studies of clinical samples showed a positive association of ER β 5 expression with a longer relapse-free survival (RFS) [38] and a significant correlation of its nuclear expression with overall survival (OS) [36]. Recently ER β 5 has also been found to confer sensitivity of breast cancer cell lines to chemotherapeutic agent-induced apoptosis [39].

ERs and ovarian cancer

In reproductive age women, ER α is present in the ovarian stroma and thecal cells, ovarian surface epithelium and in corpus luteum. For postmenopausal women, ER α is found in the ovarian surface epithelium, in epithelial inclusion cysts and in the stroma. In contrast, ER β is localized predominantly in the granulosa cells [40].

Most ovarian cancer patients express ER α and/or ER β . The expression levels of ER α are closely associated with estrogen-dependent growth, invasion and response to endocrine therapy in ovarian cancer. ER α is a direct target of the tumor suppressor microRNA (miR)-206, which is down-regulated in ER α -positive ovarian cancer cell lines and tissues. Introduction of miR-206 mimics inhibits cell

proliferation and invasion of ovarian cancer cells [41]. Recent studies show that effects of ER α in promoting ovarian cancer progression could be mediated by long non-coding RNAs, such as TC0100223, TC0101686 and TC0101441. TC0101441 was reported as an independent prognostic factor for overall survival [42]. Expression of ER α and its promoting role in ovarian cancer suggested that endocrine therapy could be an attractive treatment option. However, anti-estrogen treatment is not commonly used in ovarian cancer due to modest response rate.

ER β levels and/or the ER β /ER α ratio decreases along with ovarian carcinogenesis, indicating that loss of ER β expression may be involved in carcinogenesis. Treatment with the ER β agonist DPN or re-introduction of ER β significantly suppressed cell growth in both ovarian cell lines and xenografts [43–45]. The inhibitory effects of ER β were mediated via down-regulating total retinoblastoma (Rb), phosphorylated Rb, phospho-RAC-alpha serine/threonine-protein kinase (AKT) as well as cyclins D1 and A2, and up-regulating cyclin-dependent kinase inhibitor p21 (WAF1). In addition, ER β had a direct effect on ER α by strongly inhibiting its expression and activity.

Interestingly, some studies revealed that normal ovarian epithelium exhibited almost exclusively strong nuclear staining of ER β , while ovarian cancer tissue mostly showed cytoplasmic immunopositivity, and cytoplasmic ER β expression was shown to be an independent unfavorable prognostic factor for disease free survival [46]. Furthermore, cytoplasmic ER β 2 expression was also reported to be associated with reduced 5-year survival and chemoresistance [47]. These novel findings suggest that ER β and its isoforms may have different roles and be associated with distinct prognosis depending on their cellular localization.

ERs and prostate cancer

In addition to androgens, estrogens may also affect prostatic growth and development, as shown in ER α KO mice which display altered branching morphogenesis [48]. In the adult mouse prostate there is very little ER α expression and most of it is in the stromal compartment. ER β is expressed at high levels in prostatic epithelium in adult mice and humans. Knockout of ER β causes hyperplasia of the ventral prostate as well as increased cellular Ki67-positivity [49].

In humans, the expression of ER α is gradually increased from prostate intraepithelial neoplasia, invasive cancers to metastatic lesions at both mRNA and protein level. Studies of ER α KO mice revealed that ER α is an important determinant of prostate carcinogenesis [50]. In comparison to ER α , ER β is gradually lost during prostate carcinogenesis due to DNA promoter methylation [51]. Combined treatment of prostate cancer cell lines *in vitro* with DNA methyltransferase and histone deacetylase inhibitors have been shown to effectively restore ER β expression, with reduced proliferation and increased apoptosis [52]. Therefore, ER β has emerged as a promising new target for prostate cancer treatment.

Many trials have shown strong effects of antiestrogen for the treatment of prostate cancer. Studies showed a significant decrease in early prostate cancer progression when men were given toremifene [53]. The SERM raloxifene caused apoptosis in androgen-independent ER α (-) ER β (+) PC3 cells [54]. Additionally, raloxifene was found to inhibit growth of prostate cancer lung metastasis [55].

Although ER β is silenced or reduced in the majority of prostate adenocarcinomas, some studies showed that patients with ER β -positive cancers have a significantly decreased relapse-free survival [56].

ERs and colon cancer

Clinical and animal studies show that hormone replacement therapy (HRT) reduces the risk of colon tumor formation in females. Additionally, men are more likely to develop colorectal cancer compared with women of similar age. These findings indicate that estrogen may lower the risk for colorectal cancer. ER α mRNA levels are much lower than ER β levels and are similar between normal mucosa and tumor samples. ER β is the predominant ER in the colonic epithelium and the ER β level is lower in colon cancer compared to normal tissue. The decreased levels of ER β in colorectal cancer occurred in parallel to loss of differentiation and advanced Dukes staging. The protective role of ER β in colon cancer progression has been confirmed in *in vivo* studies in mice that spontaneously develop intestinal

adenomas (ApcMin/+) in which deletion of ER β lead to an increase in the size and number of adenomas [57] and where treatment with an ER β -selective agonist had the opposite effect [58]. Genome-wide studies of colorectal cancer cell lines re-expressing ER β showed that besides apoptosis, cell differentiation, and regulation of the cell cycle are the most affected functional consequences. ER β re-expression also down-regulates IL-6 and its downstream networks, which indicates that ER β mediated antiinflammatory mechanisms are involved in colon carcinogenesis [59]. In the same model, the oncogenic miR-17-92 and miR-200a/b were found to be strongly down-regulated upon re-expression of ER β [60].

ERs and metabolic disease

Estrogens have been clearly shown to regulate glucose and lipid metabolism using either models of estrogen-/ER-depletion or estrogen application/replacement. Estrogen deficiency promotes metabolic dysfunction predisposing to obesity, the metabolic syndrome, and type 2 diabetes (T2D). In rodents, it has been demonstrated that aromatase, the key enzyme of estrogen production, knockout (ArKO) mice display insulin resistance (IR), impaired glucose tolerance (IGT), and increased abdominal fat, which are reversible by E2 treatment [61]. Ovariectomy (OVX), resulting in low estrogen levels, leads to increased body weight, basal blood glucose and IGT which are reversible by re-introduction of estrogen [62]. Studies of ob/ob and high fat diet (HFD) fed mice, models of obesity and T2D, showed that estrogen treatment lowers body weight, improves glucose tolerance and insulin sensitivity in both mouse models [63,64]. In humans, the prevalence of early insulin resistance and glucose intolerance is higher in men than in women [65]. Postmenopausal women with estrogen deficiency were shown to have an accelerated development of visceral obesity, IR and T2D [62]. Several clinical trials involving postmenopausal women on hormone replacement therapy (HRT) demonstrated a reduced incidence of T2D, lower glucose plasma levels, and improved systemic insulin sensitivity [62,66]. It has been well documented that estrogens regulate energy homeostasis via both central and peripheral tissues (Fig. 2).

Central regulation of energy balance by estrogens

The hypothalamus is an essential area in the CNS that controls food intake, energy expenditure, and body weight homeostasis. Lesion of specific hypothalamic nuclei led to disorders of central energy homeostasis, such as the ventromedial hypothalamus (VMH) or the lateral hypothalamic area. ER α is abundantly expressed in the brain in the ventrolateral portion of the VMN, the arcuate nucleus (ARC), the medial preoptic area, and the paraventricular nuclei. ER β is found in the same hypothalamic nuclei, but its expression is significantly lower relative to ER α . ER α seems to be the major regulator of central energy homeostasis. ER α silencing in the VMN resulted in an increase of food consumption as well as reduced energy expenditure caused by diminished physical activity and impaired thermogenic responses to feeding [67]. OVX-rats and -mice treated with E2 and PPT exhibited a strong ER α -dependent inhibitory effect on eating behavior [68]. On the contrary, ER β deletion did not promote food intake and/or obesity [69].

Peripheral regulation of energy balance by estrogens

Estrogens regulate lipid metabolism in adipose tissue

Adipose tissue plays a major role in the regulation of lipid and glucose homeostasis and insulin sensitivity including via estrogen signaling. Estrogens affect adipose tissue by induction of lipolysis (e.g. due to activation of hormone-sensitive lipase, HSL) and reduction of lipogenesis, mostly by decreasing activity of lipoprotein lipase (LPL). Estrogens also increase the expression of insulin receptors in adipocytes, which enhances insulin sensitivity.

Both ER isoforms are expressed in adipose tissue. Both female and male ER α KO mice exhibit increased adipose tissue mass, IR and IGT, as well as adipocyte hyperplasia and hypertrophy [70,71] in white adipocyte tissue [72]. The role of ER β in glucose and lipid metabolism in adipocytes is less clear. ER β KO in male mice resulted in animals with a similar body weight and fat distribution, as well as lipid and insulin levels, when compared to control. However, ER β KO female mice under HFD showed a

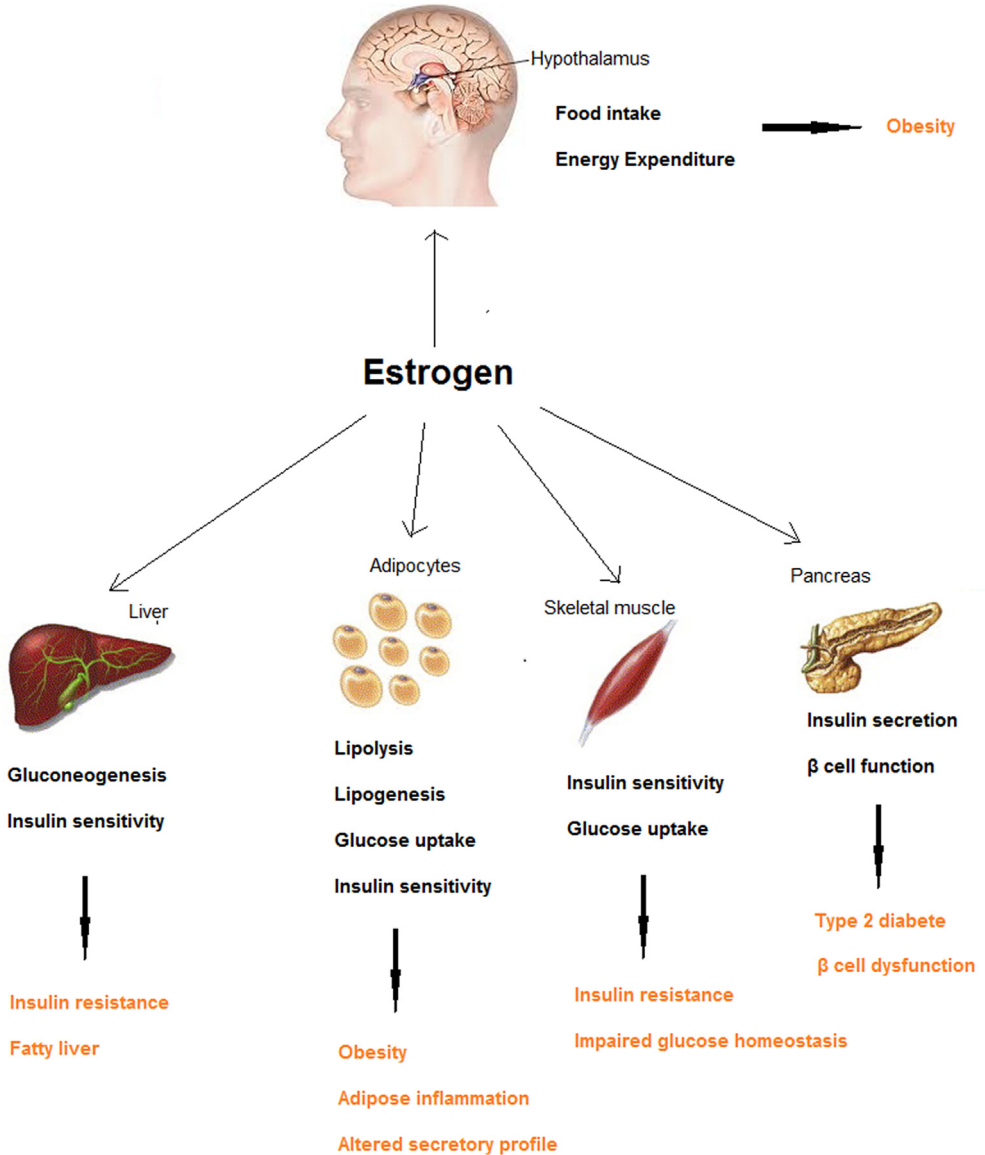


Fig. 2. Summary of estrogen actions on the central nervous system (CNS), liver, adipocytes, skeletal muscles, and pancreatic β cells. Estrogen deficiency in these tissues will contribute to metabolic dysfunction, such as metabolic syndrome, type 2 diabetes, and obesity.

higher weight gain than their wild type littermates. These effects were closely associated with a strong activation of peroxisome proliferator-activated receptor gamma (PPAR γ), a key adipogenic and lipogenic factor [73]. Recent studies of female OVX Wistar rats under HFD showed that ER β -selective agonists significantly decreased lipogenic (sterol regulatory element-binding protein- 1C (SREBP- 1c)), fatty acid synthase (FAS) and adipogenic genes (LPL, PPAR γ) in adipose tissue [74]. These findings suggested anti-lipogenic effects of ER β . Furthermore, deletion of the ER β gene protected female mice against diet-induced insulin resistance and glucose intolerance [73]. Together, both ER isoforms seem to participate in the anti-lipogenic actions of estrogens in adipose tissue.

Estrogens regulate glucose up-take in skeletal muscle

Approximately 75% of glucose clearance in response to insulin secretion is mediated by the skeletal muscle. The insulin signaling pathway that regulates glucose uptake includes insulin receptor, the insulin receptor substrate (IRS), phosphatidylinositol-3 (PI3K) and AKT kinase. Activation of this pathway eventually leads to translocation of the cytoplasmic glucose transporter 4 (GLUT4) to the cell membrane where it facilitates transport of glucose into the cell. GLUT4 is highly expressed in muscle and represents a rate-limiting step in the insulin-induced glucose uptake [75]. E2 modulates glucose homeostasis in the muscle mainly through its actions on key proteins of the insulin signaling pathway including the expression and translocation of GLUT4.

Skeletal muscle expresses both ERs, and in mice ER β is the predominant isoform. Treatment of OVX rats with PPT increases GLUT4 expression and glucose uptake in skeletal muscle [76]. PPT treatment also increases GLUT4 translocation to the cell membrane of L6 myoblasts [77]. In contrast, DPN treatment decreases GLUT4 expression in the muscle in E2-deficient ArKO male mice [78]. In summary, ER α and ER β display distinct actions on the expression of GLUT4.

Estrogens regulate metabolism in liver

Liver plays an important role in the maintenance of glucose homeostasis through glucose production by glycogenolysis and gluconeogenesis. Estrogens regulate liver glucose and lipid homeostasis and hepatic cholesterol output. Administration of E2 increased high density lipoprotein and triglycerides and decreased low density lipoprotein, total cholesterol, lipoprotein a, and fasting insulin in postmenopausal women [79]. Long term E2-treatment exhibited a major anti-diabetic effect in diabetic ob/ob mice, and decreased expression of lipogenic genes in the liver [63]. Recent studies have demonstrated that the use of antiestrogen therapy leads to abnormal lipid profile and steatosis [80].

ER α is the predominant ER isoform in hepatocytes [81]. ER α KO mice display hepatic insulin resistance, and the expression of genes involved in hepatic lipid synthesis was increased whilst expression of genes involved in lipid transport was decreased in these animals [82]. However, liver-selective ablation of ER α did not re-capitulate the metabolic phenotypes of ER α KO mice, indicating that hepatic ER α action may not be the responsible factor for the previously identified hepatic insulin resistance in ER α KO mice [83].

Estrogens regulate pancreatic β cell function

Estrogens are known regulators of pancreatic β cell function. It has rapid effects on β cells, regulating membrane depolarization, Ca $^{2+}$ influx, insulin secretion, and overall glycemia. In addition, estrogens also protect β cells from apoptosis.

Both ERs have been identified in the nucleus and cell membrane of β cells. ER α is the predominant receptor isoform for regulation of the insulin level in the pancreas. The absence of ER α results in islet dysfunction and hyperinsulinemia [82]. In β cell islets isolated from Swiss albino mice, PPT treatment increased insulin content, while DPN treatment did not [84]. Moreover, protective effects of estrogens against apoptosis were also mainly mediated via ER α . E2-treatment inhibited streptozotocin (STZ)-induced β cell apoptosis, increased insulin production, and improved insulin resistance and glucose intolerance. The protective actions of E2 were abrogated in ER α KO female mice [85]. Furthermore, estrogens regulate the ATP-sensitive potassium (K $_{ATP}$) channels in β cells [86]. Closure of K $_{ATP}$ channels is a pivotal event in the glucose-induced insulin release. Once the channel is closed, membrane depolarizes and insulin is released. The main function of ER β in β cells seems to be a rapid regulation of K $_{ATP}$ channel and insulin secretion, as it showed that E2 and DPN reduced the activity of K $_{ATP}$ channels in β cells from wild type and ER α KO mice, but not in those from ER β KO mice [86].

Hormone replacement therapy in metabolic diseases

Pharmacological estrogens can reverse the progression of metabolic diseases. Estrogens have been approved by FDA for postmenopausal therapy. However, due to ubiquitous expression of ERs, the metabolic benefits provided by HRT are often associated with increased risk of heart disease, gynecological and breast cancer. One strategy to make estrogens therapeutically more efficient is to develop novel tissue selective SERMs. Another approach is to design novel molecules that would direct E2 to

target tissues without the undesirable effect of general E2 therapy. Recent reports on the development of a glucagon-like peptide-1 (GLP-1)-estrogen conjugate, which uses a peptide carrier to deliver estrogen selectively to specific tissues, showed high efficacy and much less side effects [87].

Summary

Estrogens play important roles in physiological processes via both ER α and ER β . Abnormalities in estrogen signaling lead to different types of pathological conditions, such as cancer and metabolic diseases. In general, ER α expression increases at early stages of cancer, and acts as a tumor promoter. Antiestrogens are widely used for the treatment of breast cancer. On the contrary, ER β levels are reduced during carcinogenesis and cancer progression, and act as a tumor suppressor. Accordingly, ER β is a promising potential target for cancer therapy. However, some contradictory findings regarding the expression and functions of ER β in cancer have been reported. Such discrepancies could reflect heterogeneity of patient populations. They may also be due to high heterogeneity of breast tissue, and low correlation between ER β mRNA and protein levels. Thus, there is a clear need to further study the roles of ER β in cancer.

Estrogens play important roles in maintenance of lipid and glucose homeostasis. They centrally regulate food intake and energy expenditure via action on the CNS, and they also act on peripheral tissues to maintain energy homeostasis. ER α and ER β play distinct role in insulin and glucose metabolism. The major concern in using therapies targeting ER in treatment of metabolic disease is the risk of achieving undesirable effects. Further studies are needed to identify and develop new molecules that target ERs in selective metabolic tissues.

Practice points

- The presence of ER α is an important indicator for use of hormone therapy for breast cancer treatment.
- The use of antiestrogens such as tamoxifen, raloxifene, fulvestrant, anastrozole, letrozole or exemestane is recommended against ER α -positive breast cancer.

Research agenda

- The role of ER α and ER β in cancer and metabolic disorders, and their potential for clinical applications need to be clarified.
- The mechanisms of resistance to antiestrogen treatment in breast cancer must be further investigated.
- New effective tissue and receptor selective antiestrogens should be identified.

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