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Estrogen: The necessary evil for human health, and ways to tame it

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ABSTRACT

Estrogen is a pivotal enzyme for survival and health in both genders, though their quantum, tropism, tissue-specific distribution, and receptor affinity varies with different phases of life. Converted from androgen via aromatase enzyme, this hormone is indispensable to glucose homeostasis, immune robustness, bone health, cardiovascular health, fertility, and neural functions. However, estrogen is at the center of almost all human pathologies as well-infectious, autoimmune, metabolic to degenerative. Both hypo and hyper level of estrogen has been linked to chronic and acute diseases. While normal aging is supposed to lower its level, leading to tissue degeneration (bone, muscle, neural etc.), and metabolite imbalance (glucose, lipid etc.), the increment in inflammatory agents in day-to-day life are enhancing the estrogen (or estrogen mimic) level, fueling 'estrogen dominance'. The resultant excess estrogen is inducing an overexpression of estrogen receptors (ERα and ERβ), harming tissues, leading to autoimmune diseases, and neoplasms. The unprecedented escalation in the polycystic ovary syndrome, infertility, breast cancer, ovary cancer, and gynecomastia cases are indicating that this sensitive hormone is getting exacerbated. This critical review is an effort to analyze the dual, and opposing facets of estrogen, via understanding its crosstalk with other hormones, enzymes, metabolites, and drugs. Why estrogen level correction is no trivial task, and how it can be restored to normalcy by a disciplined lifestyle with wise dietary and selective chemical usage choices has been discussed. Overall, our current state of knowledge does not disclose the full picture of estrogen's pleiotropic importance. Hence, this review should be a resource for general public as well as researchers to work in that direction.

1. Introduction

Estrogen is more than just an estrus-inducing sex hormone. In fact, this steroid hormone controls almost all aspects of female and even male health [1]. Critical functions like glucose homeostasis, lipid homeostasis, bone metabolism, brain function, follicular growth, skeletal growth, and ovulation, among a myriad other functions, depend on its signals [1,2]. Estrogens (C18) are formed by the demethylation of androgens (C19), the male hormone precursors [3]. Aromatase, a cytochromes P450 (CYP) class monooxygenase enzyme, encoded by CYP19 gene is extremely critical for estrogen biosynthesis [4–6]. Aromatase is responsible for the aromatization of androgen into estrogen. Most of the estrogen perturbation-caused ailments as breast cancer, polycystic ovary syndrome (PCOS), endometriosis, osteoporosis, ovarian cancer, gastric cancer, pituitary cancer, Alzheimer's disease, schizophrenia, male hypogonadism, and transgender issues, are linked to aromatase malfunction as well [3]. The same estrogen ligands when bound to different receptors, exert different physiological functions by autocrine or paracrine mechanisms, of which some are beneficial for the body, and some are detrimental [7]. Considering the gamut of diseases that are linked to estrogen, hormonal replacement therapy (HRT) is a common therapeutic option [8], which however is not side-effect-free. In both genders, the depletion of estrogen can lead to digestive issues, osteoporosis, Alzheimer's disease *etc*. In fact, it can be argued that chemotherapy blocking the essential estrogen signals lead totoxicity-related death in cancer patients. This critical review discusses the indispensable, dual and antagonizing function of estrogen in human body.

2. Estrogen and its receptors

Aromatase activity varies in different parts of the body, so does estrogen. Adipose tissues are the predominant steroidogenesis sites. Apart from ovary, placenta, and breasts, estrogens can occur in skin,

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bone, brain, liver, and adrenal glands [9]. Gender, age, and health status are factors deciding estrogen level in the body [10]. Puberty is a phase where estrogen level is high in females, which mediates sexual differentiation [11].

Estrogen (17 beta-estradiol) exerts its diverse functions by ligating to the nuclear hormone receptor protein, a form of transcription factor [12]. These classes of receptors are critical for the embryonic development, cell differentiation and homeostasis. Estrogen receptors (ER) occur in the nucleus, cytoplasm, and mitochondria of cells, and as a result of alternative splicing of the transcripts, they can be of several types. The two dominant types are alpha, and beta, which further occur in multiple isoforms. Alpha type ER (ERα) was discovered first, followed by the rather recent discovery of beta-type ER (ERβ). *In silico* analysis of the ERs from both types showed the presence of common domains/motifs *i.e.* N-terminal DNA binding domain, and C-terminal ligand binding domain [13]. As per the SMART (Simple Modular Architecture Research Tool)-based *in silico* analysis of some ER sequences retrieved from UniProt, both human ERα and ERβ had ZnF_C4 domain (c4 zinc finger) [14,15]. Zinc finger (Znf) domains are small DNA-binding motif with variation in binding modes. The classes under the Znf superfamily include ZnF_BED, ZnF_A20, ZnF_NFX *etc*. [16,17]. Homologues of all these zinc finger motifs have been detected in pathogenic viruses like HCV, HIV, and dengue. Another oft-occurring domain in these ERs include HOLI. This is a ligand binding domain of hormone receptors [18]. Further analysis showed that androgen receptor has a coiled-coil region, along with the above 2 domains. Glucocorticoid receptor has a HOLI domain; thyroid hormone receptor beta has ZnF_C4, and HOLI; Insulin-like growth factor 1 receptor has transmembrane region; G-protein coupled estrogen receptor 1 has 7 transmembrane regions. So, almost all the steroid receptors share the same motifs. Some other domains in the ERs with less-confident scores included Mcm10, ICA69, TR_THY, APC10, IL4_13, MAGE_N, AMA-1, B_lectin, Thymopoietin, C6, IBR, BowB, ZnF_GATA, IB, zf-AD, RPOLCX, PHD, RING, ZnF_NFX, LU, LDLa, C1_4, RINGv, ZnF_RBZ, SR, LRRCT, RGS, MADF, HTH_MARR, Rapamycin_bind, HTH_ARSR, BSD, FerA, CarD_TRCF, WH2, IDEAL, and ZM [15]. These domains regularly occur in pathogenesis-associated proteins from the organisms of diverse kingdoms [15,19]. It is suggested that all these virulence-associated domains have radiated from the same parent domain.

However, sequence variations in other parts of the ER proteins lead to different affinity for the estrogen. Once bound to the ligand estrogen, the ER becomes dimeric, and bind to estrogen response elements of DNA, regulating transcription [20]. The N-terminal DNA-binding domain of the ERs can elicit activating or repressing effects. On ligation with the ERs, estrogen acts as a mitogen, promoting cell division, neoplastic transformation and proliferation. Activity of estrogen is more pronounced in those tissues where its receptors are abundant, such as ovary, breast, brain (hypothalamus), kidneys, bone (bone marrow) *etc*. By binding to its receptors in the hypothalamus, it regulates anorexigenic/orexigenic stimuli, controlling food intake and glucose level.

Tissue distributions of both the ER types differ. As per the current state of knowledge, ERα occurs in the female reproductive system, while ERβ occurs in the prostate, colon, cardiovascular, and central nervous systems. Skeletal muscle expresses both ERs.

The antagonistic functions of ERα and ERβ have been documented. They have some common functions as well, but they regulate unique sets of genes, as revealed from microarray experiments [21]. ERα is the main regulator of GLUT4 (glucose transporter type 4) expression in adipose tissues, while ERβ is the repressor of the protein [22]. ERα induced leptin expression while ERβ inhibited its expression in 3T3-L1 adipocytes [23]. Leptin is a 16 kDa peptide formed by the white adipocytes, and is required for homeostasis [24]. This adipokine causes cardiac hypertrophy (thickening of myocardium) [25]. Leptin, along with adiponectin, and hepatocyte growth factor (HGF), enhances aromatase expression and inflammation [26–28].

ERα overexpression is a hallmark of estrogen +ve breast cancer [29]. ERα has ameliorative effects following trauma-hemorrhage [30]. Hyperinsulinemia activates DNA methyltransferases, which decrease ERα expression via their gene methylation [31]. ERα-ligated estrogen stimulates cell proliferation and induces neoplastic transformation [32].

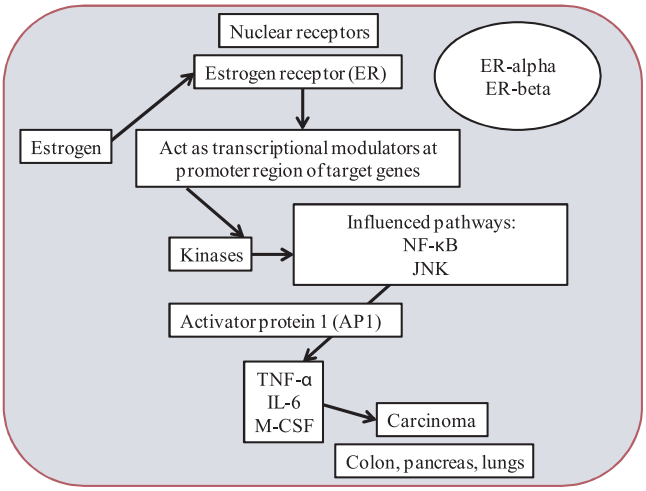

Fig. 1. Estrogen-ER complexation and the pathways activated. As the ligand estrogen binds to the ERs, they act as transcription regulators. The activated ER regulates the activation of the proinflammatory transcription factor NFκB. NFκB pathway activation induces M-CSF production which plays role in macrophage transformation by upregulating c-Jun, a major component of the transcription factor activator protein (AP)-1. Jun amino-terminal kinase (JNK), which phosphorylates c-Jun, is activated by the ligand-receptor complex as well. AP-1 induces the elaboration of the inflammatory cytokine TNF-alpha, which increases VEGF expression in breast cancer cells.

Polymorphism in ERβ has been associated with endometrioid carcinoma [33]. ERβ has been observed in TNBC (triple negative breast cancer) cell lines (MDA-MB-453, SUM-185-PE and MFM-223) [34].

A study reports that the net action of estrogen is an outcome of the relative ratio of each ER type [35]. The ERs and the pathways activated followed by estrogen binding has been presented in Fig. 1. Functions of ERs have been discussed in later sections as well, as the context required. Though much remains to be known about the role of both receptor types, Table 1 presents a list of pathologies and the dominant ER types.

3. Estrogen imbalance and consequent diseases

Both hyper and hypo level of estrogen sets off a diverse array of diseases *i.e.* autoimmune, metabolic, neural, and gender-specific, among others [12]. The section below briefly narrates the common pathologies, resultant of perturbed estrogen level. Also, the pathologies resultant of estrogen perturbation have been presented in Fig. 2 and Table 2.

3.1. Hyper-estrogen activity-driven pathologies

High estrogen level is causal of numerous health issues, some key of which have been discussed here. Polycystic ovary syndrome (PCOS) is characterized by the endocrine disturbance, leading to cysts in the

Table 1
Pathologies and the dominant ER types.

ER type	Pathologies	References
ERα	Thyroid tumors	[52]
	ER +ve breast cancer	[29]
ERβ	Endometrioid carcinoma	[33]
	Triple negative breast cancer	[34]