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Estrogen receptor alpha and beta in health and disease

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Estrogen receptors alpha (ERα) and beta (ERβ) 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 ERα and ERβ 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.

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 17β-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, ERα and ERβ.

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. ERβ, was cloned from the rat prostate and ovary in 1996 [2]. ERα is mainly expressed in reproductive tissues (uterus, ovary), breast, kidney, bone, white adipose tissue and liver, while expression of ERβ 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 ERα and ERβ genes are located on different chromosomes, 6q25.1 and 14q23.2, respectively. ERs are composed of three functional domains: the NH_2-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 ERα and ERβ. The DBD is highly conserved between ERα and ERβ 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 ERα and ERβ 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 ERα and ERβ selective agonists, respectively. The LBD also contains a ligand-dependent activation domain (AF2).

Due to alternative splicing of ER-mRNAs, three ERα isoforms have been identified (Fig. 1). ERαΔ3 lacks exon 3, which encodes part of the DNA-binding domain [3]. ERα36 lacks both AF-1 and AF-2, and the last 138 amino acids (aa) are replaced with a unique 22 aa sequence [4]. ERα46 lacking aa 1-173

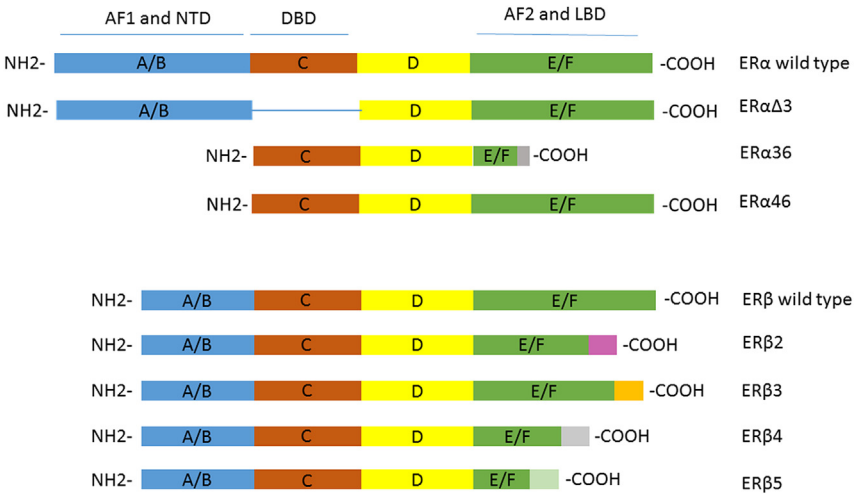

Fig. 1. The structures of the ER isoforms. Different functional domains are highlighted: the NH_2-terminal domain (NTD) in blue, DNA-binding domain (DBD) in orange, and the COOH-terminal or ligand-binding domain (LBD) in green. The NTD contains a ligand-independent activation function (AF1) region which is responsible for recruitment of co-regulatory proteins.