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Gene Section
Mini Review

ESR2 (Estrogen Receptor 2 (ER beta))

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Identity

Other names: ESRB; ESR-BETA; ESTRB; ER-BETA; Erb; NR3A2
HGNC (Hugo): ESR2
Location: 14q23.2

DNA/RNA

Description

ER beta gene consists of 8 encoding exons. The open reading frame of the coding region is 1,593 bp.

Protein

Description

The full-length human ER beta protein is 530 amino acids; 59.2 KDa, is also named ER beta1. Another isoform, ER beta2, is formed by alternative splicing of the mRNA. ER beta2 encodes a protein of 495 amino acid residues, with a molecular weight of 55.5 kDa. ER beta2 has a unique C-terminus, where the amino acids corresponding to exon 8 are replaced with 26 unique amino acids.

Expression

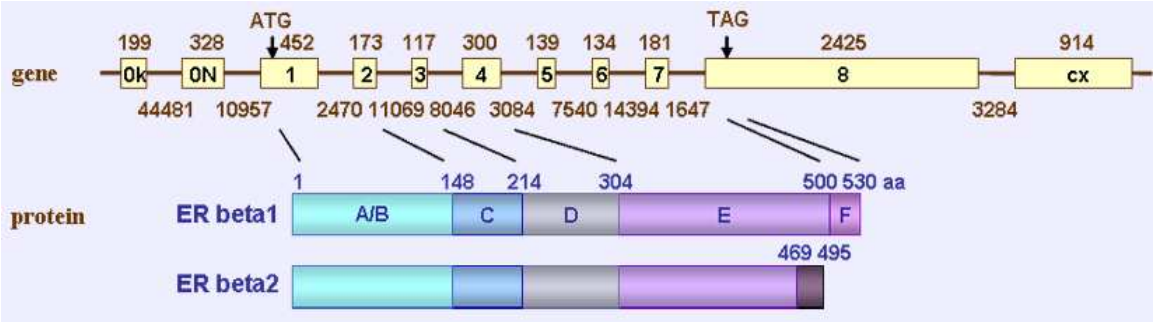
ER beta is mainly expressed in tissues such as the ovary (granulosa cells), prostate (epithelium), testis, epididymis, colon, lung, bladder, bone marrow, salivary gland, vascular endothelium and regions of the brain, including hypothalamus and cortex.

Localisation

Nucleus.

Function

Cellular signaling of estrogen is mediated through two estrogen receptors (ERs), ER alpha and ER beta. The first ER, now known as ER alpha, was cloned in 1986. This receptor was regarded as the only ER that mediates estrogenic effects, until a



Genomic organization of human ER beta gene, protein and functional domains.
Gene: exons are indicated with boxes and introns with lines. The numbers above each box indicate the size of the exons (bp); the numbers below each line designate the size of the respective introns (bp). Dotted lines between gene and protein point to protein domain junctions.
Protein: numbers indicate the total size of the protein in amino acids. The shaded bar shows the divergent C-terminal regions between the isoforms.

second ER, now known as ER beta, was cloned from rat prostate. ER alpha and ER beta belong to the superfamily of nuclear receptors and specifically to the family of steroid receptors that act as ligand-regulated transcription factors. ER alpha and ER beta have a high sequence homology and share affinity for the same ligands and DNA response elements.
Binding of ligand activates ERs, by a mechanism that involves dissociation of heat shock proteins and dimerization of receptor proteins. Estrogen-modulated gene transcription is exerted via different mechanisms: the genomic and the nongenomic pathways. The canonical model for ER-mediated regulation of gene expression involves the direct binding of dimeric ER to DNA sequences known as estrogen response elements (EREs), followed by recruitment of a variety of coregulators to alter chromatin structure and facilitate recruitment of the RNA polymerase II (Pol II) transcriptional machinery.
The transcriptional activity of ERs can be modulated by different types of post-translational modifications such as phosphorylation, acetylation, sumoylation, ubiquitination and methylation. ER alpha and ER beta exhibit different affinities for some natural compounds, and distinct expression patterns in a variety of tissues. Transcriptional activation by ER alpha is mediated by two distinct activation functions: the constitutively active AF-1 and the ligand-dependent AF-2. ER beta seems to have a weaker corresponding AF-1 function and thus depends more on the AF-2 for its transcriptional activation function. ER alpha and ER beta have different activities in certain ligand, cell-type, and promoter contexts.

Homology

Chimpanzee (Pan troglodytes), dog (Canis lupus familiaris), cow (Bos taurus), mouse (Mus musculus), rat (Rattus norvegicus) chicken (Gallus gallus), zebrafish (Danio rerio).

Implicated in

Various cancers

Note

Targeted disruption of ER beta in mice has suggested roles for ER beta in many tissues and organs, including the ovary, uterus, mammary gland, brain, immune system and ventral prostate.

Prostate cancer

Disease

Estrogens can have profound effects on prostate growth and differentiation as well as in the pathogenesis of prostate cancer. In the adult rodent ventral prostate, ER beta is expressed in the epithelial cells, whereas ER alpha is expressed in the stroma. The estrogenic effects in the prostate may therefore be exerted by both ERs but in different cells. ER beta knockout mice display signs of prostatic hyperplasia with aging.

Breast cancer

Disease

Estrogen is essential for growth and development of the mammary glands, and has been associated with promotion and growth of breast cancer. ER beta is found in both ductal and lobular epithelial and stromal cells of the rodent, whereas ER alpha is only found in the ductal and lobular epithelial cells and not in stroma. Recent studies have indicated a protective role of ER beta against breast cancer development. In vitro studies indicated that ER beta is an important modulator of proliferation and invasion of breast cancer cells.

Colon cancer

Disease

ER beta is the predominant ER in the colonic epithelium, suggesting that effects of estrogen in the colon are mediated by ER beta. In colons from ER beta knockout mice, the number of proliferating cells was higher, and the migration of labelled cells from base to lumen of the crypts was faster when compared to wild-type mice. Additionally, immunohistochemical staining revealed fewer apoptotic cells (cleaved caspase 3-positive), a significant decrease in expression of the epithelial differentiation marker, cytokeratin CK20, the adherens junction protein, alpha -catenin, and the hemidesmosomal protein, plectin, in ER beta knockout mice. These findings suggest a role for ER beta in the organization and architectural maintenance of the colon.

Ovarian cancer

Disease

A loss of ER beta expression or a decrease in ER beta/ER alpha ratio in epithelial ovarian cancer cells as compared with normal tissues has been reported by several groups. ER beta overexpression in ovarian cancer cells has been reported to exert antitumoral effects.

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