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Gene Section
Mini Review

IGF1R (insulin-like growth factor 1 receptor)

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Identity

Other names: CD221; IGFIR; JTK13; MGC142170; MGC142172; MGC18216

HGNC (Hugo): IGF1R

Location: 15q26.3

DNA/RNA

Description

The IGF1R gene contains 21 exons spanning approximately 100-kb of genomic DNA.

Transcription

The IGF1R mRNA is a 11242-base, single-stranded linear molecule. Various hormones and growth factors were shown to regulate IGF1R gene transcription. Specifically, growth factors and oncogenic agents associated with positive stimulation of cell division were shown to upregulate IGF1R gene expression whereas negative modulators of cell growth (e.g., tumor suppressors) usually cause a reduction in IGF1R gene expression. Growth factors that stimulate IGF1R gene transcription include, among others, basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF). In addition, IGF1R gene expression is regulated by steroid hormones. Thus, estradiol was shown to increase, while progesterone decreased, IGF1R mRNA levels in breast cancer cells.

Protein

Description

The IGF1R is a cell-surface tyrosine kinase receptor that is synthesized as a single polypeptide chain which is then processed to yield an around 180-kDa glycopeptide. The length of the IGF1R precursor is 1367 amino acids. Precursor chains include a 30-amino acid leader peptide rich in hydrophobic residues, which is involved in the transfer of the nascent protein into the endoplasmic reticulum. Partially processed proreceptors form disulfide-linked dimers that are subsequently glycosylated and proteolytically cleaved at a basic tetrapeptide sequence to yield mature α and β subunits. The mature heterotetramers have a β-α-α-β conformation.

The α subunit is entirely extracellular and includes a cysteine-rich region and several potential N-linked glycosylation sites (Asn-X-Ser/Thr motifs). The cysteine-rich domain of the IGF1R is important for high-affinity IGF1 binding.

The β subunit features a unique hydrophobic sequence that constitutes the transmembrane domain. The cytoplasmic portion of the β subunit contains a tyrosine kinase enzymatic domain. Inside this catalytic region there is a glycine-rich conserved element that participates in the transfer of the phosphate moiety of ATP to specific substrates.

Expression

The IGF1R is abundantly expressed in the embryo, with significant reduction in expression levels at adult stages.

Localisation

The IGF1R is essentially expressed by most organs and tissues. Very high levels are detected in brain. Extremely low levels are seen in liver, due to downregulation by hepatic IGF1.

Function

The IGF1R is involved in growth, development, and differentiation processes. The IGF1R displays a very

strong antiapoptotic activity and protects IGF1R-expressing cells from programmed cell death.
IGF1R is vital for cell survival, as illustrated by the lethal phenotype of mice in which the IGF1R gene was disrupted by homologous recombination. During normal ontogenesis, the IGF1R is expressed at every developmental period, including the oocyte stage. Late embryonic and adult stages, in which the percentage of rapidly proliferating cells declines, are associated with an overall reduction in IGF1R mRNA levels.
IGF1R is involved in normal growth, development, and differentiation processes. IGF1R mediates the biological roles of both the IGF1 and IGF2 ligands. IGF1R binds IGF1 and IGF2 with high affinity, and insulin with significantly reduced affinity. IGF1R displays a very potent antiapoptotic activity, protecting IGF1R-expressing cells from programed cell death. Activation of the IGF1R by locally-produced or circulating IGF1 or IGF2 leads to autophosphorylation of the tyrosine kinase domain, with ensuing activation of the Ras-Raf-MAP kinase and PI3K-PKB/Akt signaling pathways. Activation of these cytoplasmic mediators is critical in order for the IGF1R to exert its mitogenic and antiapoptotic activities.
The biological actions of the IGF1R are modulated by a family of IGF-binding proteins (IGFBPs) that includes at least six members (IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6). IGFBPs control IGF1R action by regulating the bioavailability of the IGF1 and IGF2 ligands. The affinity of the IGFBPs for the ligands is 1-2 orders of magnitude higher than the affinity exhibited by the receptor. IGFBPs usually display inhibitory types of activities however, under certain circumstances, IGFBPs may also stimulate IGF1 action.

Mutations

Note

IGF1R mutations are very rare, suggesting that homozygous mutations are a lethal condition. Recently, IGF1R mutations were described in two cohorts of children. The first cohort consisted of children with unexplained intrauterine growth restriction and subsequent short stature, and the second group included children with short stature and high circulating IGF1 levels. A compound heterozygote for point mutations in IGF1R exon 2 was identified in a girl from the first group. Fibroblasts cultured from the patient had decreased IGF1R binding and IGF1-stimulated phosphorylation. In the second cohort a boy was identified with a nonsense mutation, leading to reduced IGF1R expression.
In a family harboring a ring chromosome 15, hemizygotes for the IGF1R locus showed severe growth failure, while a patient possessing two copies of the gene had borderline stature. On the other hand, a patient with three IGF1R gene copies due to a partial duplication of the long arm of chromosome 15, presented with height and weight above the 97th percentile and showed accelerated cellular growth.

Implicated in

Various tumors

Note

Clinical and experimental data collected over the past 25 years have suggested that the IGF1R gene exhibits a pattern of expression in malignant cells that reflects its pro-survival role. Using a variety of techniques, including IGF binding and radio-receptor assays, Northern and Western blottings, and immunohistochemical and in situ hybridization analyses, most studies consistently showed that the IGF1R is expressed at high levels in primary tumors and cancer-derived cells. These tumors include, among others, breast, prostate, ovarian, colon, hematopoietic, rhabdomyosarcoma, and renal cancers. These augmented IGF1R levels reflect a reversal to more primitive, less differentiated, ontogenetic stages that, in most species and body organs, are characterized by very high concentrations of IGF1R mRNA and IGF binding sites. Whereas the molecular mechanisms that lead to increased IGF1R gene expression in cancer remain largely unexplained, the dogma that emerged postulated that IGF1R expression is a fundamental prerequisite for cellular transformation. The appeal of this paradigm resides in the fact that enhanced IGF1R levels and IGF1 signaling are considered key factors, indispensable for the cell, in order to adopt proliferative/oncogenic pathways.
Anti-IGF1R strategies (e.g., humanized IGF1R antibodies, low molecular weight tyrosine kinase inhibitors, etc.) are currently being developed in order to target the IGF1R as a clinically relevant therapeutic target.

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