

Gene Section

Short Communication

IGF1 (Insulin-Like Growth Factor 1 (Somatomedin C))

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Abstract

Short Communication on IGF1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: IGF-I, IGF1A, IGFI

HGNC (Hugo): IGF1

Location: 12q23.2

DNA/RNA

Description

Genomic size: 84779 bp. The IGF-1 Gene is

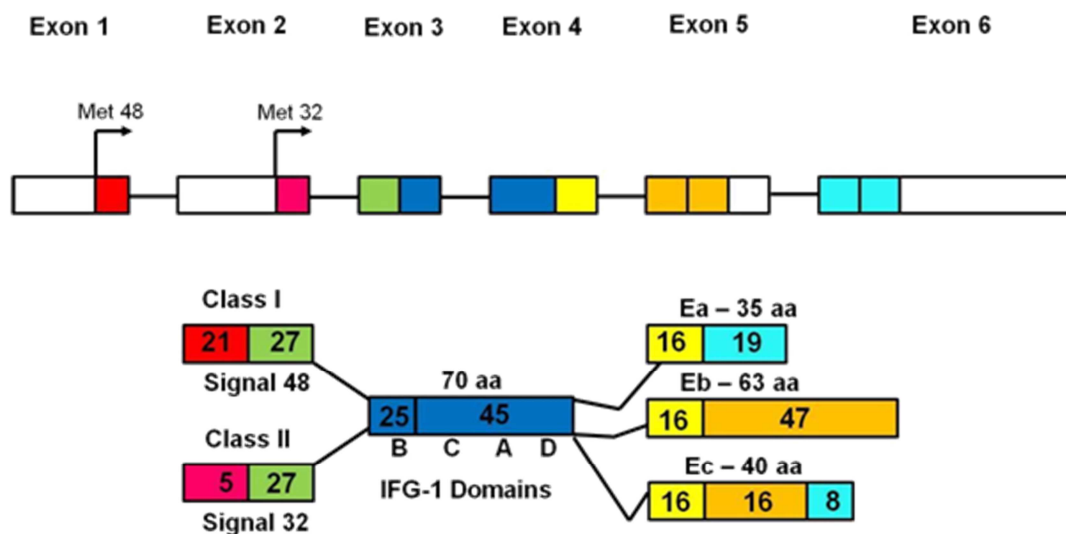
composed of 6 different exons.

Exons 1 and 2 determine the class of the protein and functionally represent the signal peptide for cellular localization post-translation.

Exons 3 and 4 will primarily encode the IGF-1 mature peptide; ultimately becoming the receptor binding ligand.

Exons 5 and 6 will primarily represent the E domain peptide; with exon six providing the different polyadenylating signals.

These parts of the transcript give a functional distinction to the 6 isoforms produced (although such distinctions have yet to be definitively identified) (Adapted from Mills et al., 2007; Philippou et al., 2007).



Illustrates IGF-1 splice sites and isoform variants (adapted from Mills et al., 2007).

Transcription

Six different heterogeneous mRNA are transcribed using alternate promoters, alternate splice sites and varying polyadenylation signals. Class one and two are derived from the exon one and two promoter respectively; both are differentially spliced to the common three exon. Each class can be variably spliced to the fifth and sixth exons, producing a total of six different isoforms (Philippou et al., 2007).

Class one isoforms predominate in the extrahepatic tissues and are secreted in a paracrine/autocrine fashion.

Class two isoforms predominate in the liver and are secreted in an endocrine fashion. They are also more sensitive or responsive to growth hormone relative to class 1 (Mills et al., 2007).

Individual isoforms may be more favorably translated depending on the tissue type, the available binding proteins and the physiological context.

Researchers are discovering evidence that suggest certain isoforms may be preferentially expressed under varying amounts of mechanical pressure in skeletal muscle (Philippou et al., 2007). The advantages of one isoform or another, in varying contexts of stress, inflammation, regeneration and hypertrophy are yet to be elucidated.

Pseudogene

Not reported.

Protein

Description

Single polypeptide chain protein consisting of 70 amino acids and three disulfide bridges.

Expression

It is primarily produced and secreted in endocrine fashion by the liver. It is also produced and secreted in autocrine or paracrine fashion in a wide range of extra-hepatic tissues. Tissues produce IGF-1 protein in response to growth hormone during periods of pre/post-natal development, exercise and injury. Inhibited in undernourished states, low protein, growth hormone deficiency and growth hormone receptor insensitivity (Cheng et al., 2006).

Localisation

The protein is post-translationally modified by protease cleavage of the signal and E-peptide. The mature protein subsequently binds to one of six binding proteins and is then secreted from the tissue of origin (IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6). IGFBP3 predominates, binding to 80% of the available IGF-1. The binding proteins increase the half life of IGF, preventing renal

clearance and inactivation. IGFBP (1,3,4,6) are growth promoting; IGFBP-(2,5) bind IGF-1 and limit IGFR/IGF-1 interaction; a growth inhibiting effect.

Function

Important for growth/development in children and adults. Vital role in anabolic processes in general. Important functions in osteogenesis, axonal generation in nerves, nerve regeneration after ischemic insult, muscle repair and hypertrophy after trauma or exercise (Cheng et al., 2006). Although still under investigation, studies suggest that individual isotype/binding protein combinations manifest in response to specific environmental interactions or physiological demands. In addition, the binding proteins are critical for maintaining the bioavailability of the IGF-1. The unique IGF-1/IGF-1 receptor complex will then signal the protein cascade necessary for tissue metabolism or regeneration. Ischemic damage to the brain illustrates how this concept materializes. Cytotoxic edema and inflammatory markers induce the transcription of a specific isotype; which then binds to a tissue specific binding protein; protecting the integrity of the protein and preventing its renal clearance. The distinctive IGF-1/IGF-1R complex will then activate the protein kinase cascade necessary for axonal regeneration.

Cellular/molecular effects: Upon binding, the tyrosine kinase receptor, IGF-1/IGF-1R complex activates the PI3K/AKT/mTOR and RAS/RAF/MAPK protein cascades. Both interfere with apoptosis and are pro-cell survival; the latter additionally promotes cellular differentiation, metabolism, growth and repair. Given its integral utility in tissue growth, repair and cell cycle regulation, IGF-1 receptors are found ubiquitously throughout the body and include: muscle, bone, cartilage, kidney, liver, lung and nervous tissue (Schiaffino et al., 2011).

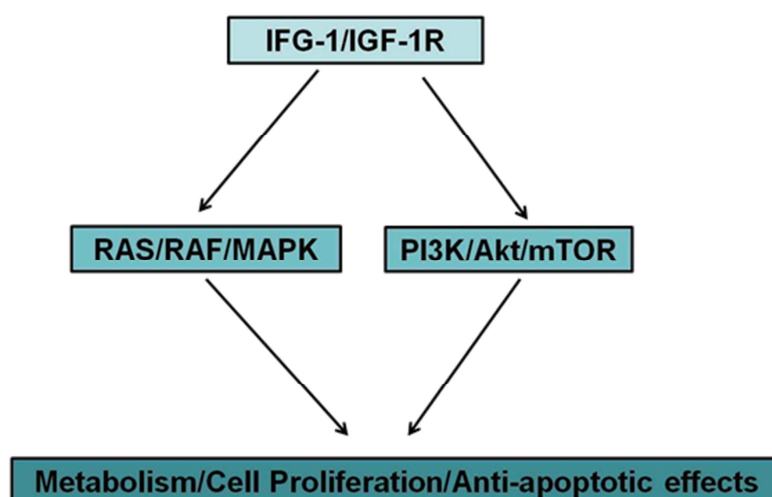
It is speculated that binding proteins may not only enhance or subdue IGF-1/IGF-1R interaction but help specify which isoform should predominate.

Biotech and Clinical Application: Recombinant IGF-1 expressed in *e. coli* is being tested either for symptomatic relief, tissue regeneration or penetrance reduction in the following diseases or conditions:

- Laron's Dwarfism
- Duchenne's Muscular Dystrophy
- Amyotrophic Lateral Sclerosis
- Post ischemic damage to brain (stroke)
- Diabetes and Insulin Insensitivity

Homology

Shares some sequence homology to insulin and has a relatively weak affinity to insulin receptors.



IGF-1 mediated signal transduction (adapted from Schiaffino, S. et. al, 2011).

Implicated in

Various cancers

Note

No specific mutations of IGF-1 have been connected to genetically acquired diseases. Despite this fact, certain haplotypes of IGF-1 have been implicated in the survival of solid tumors. It is postulated that IGF-1 has tumor promoting effects when its cellular growth/anti-apoptotic functions become dysregulated (see oncogenesis below). Additionally it plays a critical role in the clinical sequelae of Laron's dwarfism (see below).

Disease

High levels implicated in the survival of solid tumors and Acromegaly. Low levels of IGF-1/IGFBP3 consistently found in Laron's Dwarfism; An Autosomal recessive disease caused by a mutation in the growth hormone receptor; causing poor ligand interaction with growth hormone and subsequent low levels of IGF-1.

Prognosis

Individuals with Laron's are dwarfs with characteristic facial and anatomical anomalies (flat nasal bridge, prominent forehead, obesity, small mandible and phallus). They also exhibit seizures secondary to hypoglycemia. Unlike Achondroplasia, Laron's Dwarfism does not respond to GH. Laron Dwarfs have a greater resistance to diabetes, cancer and age progression; underscoring the function of IGF-1 and its critical role in cellular metabolism and cell cycle maintenance (Melnik et al., 2011).

Oncogenesis

IGF-1 signaling through RAS/RAF/MAPK and has been demonstrated to promote breast cancer and prostate tumorigenesis. IGF-1/IGF-R interaction induces the transcription of survival/ growth

enhancing genes. Signaling through these pathways results in increased cellular proliferation and anti-apoptotic effects; promoting a favorable environment for tumor growth.

In General, high levels of IGF-1 are found in solid tumors (particularly breast and prostate). Certain SNP's and IGF-1 haplotypes have been associated with increased risk of colon, pancreatic, prostate and breast cancer.

It is likely that specific haplotypes in combination with other variables can create a more favorable tumorigenic environment. i.e. Individuals with a BMI>25, containing specific IGF-1 haplotypes may have a greater risk of developing pancreatic cancer (Cheng et al., 2006).

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