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Gene Section
Review

FGF1 (fibroblast growth factor 1 (acidic))

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Abstract

Review on FGF1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: AFGF, ECGF, ECGF-beta, ECGFA, ECGFB, FGF-1, FGF-alpha, FGFA, GLIO703, HBGF-1, HBGF1

HGNC (Hugo): FGF1

Location: 5q31.3

DNA/RNA

Description

The FGF1 gene is located chromosome 5 from 141971743 to 142077617 (105893 bp) on the minus strand.

Transcription

The FGF1 gene has 12 splice variants shown in Ensembl database. Nine of transcripts are protein-coding isoforms and 3 of those have no protein product.

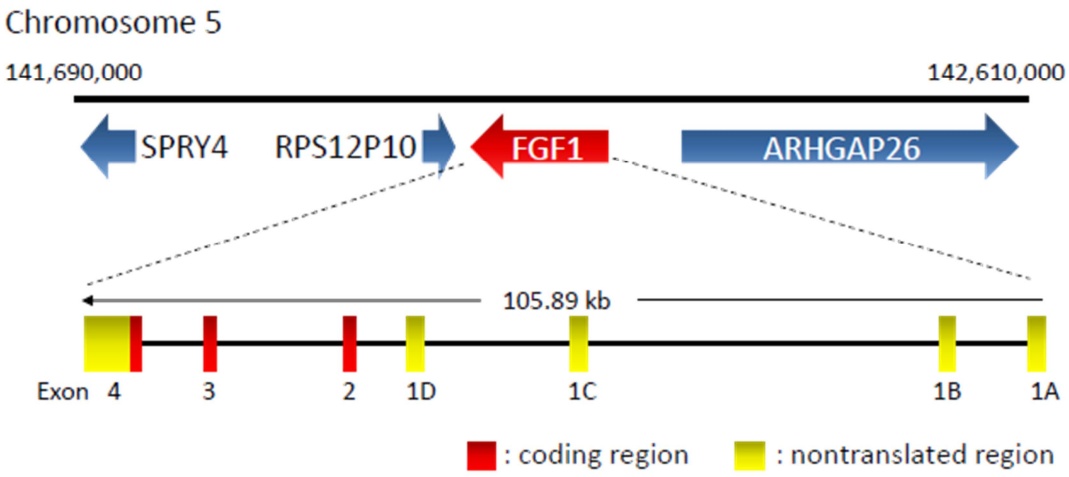

Figure1. FGF1 gene spans 105,89 kb on chromosome 5 in the region of q31.3 on the minus strand. It consists of 3 coding exons and 4 untranslated exons. The transcription is regulated by four distinct promoters. These are separated in the different 5' untranslated exons, designated 1A, 1B, 1C and 1D.

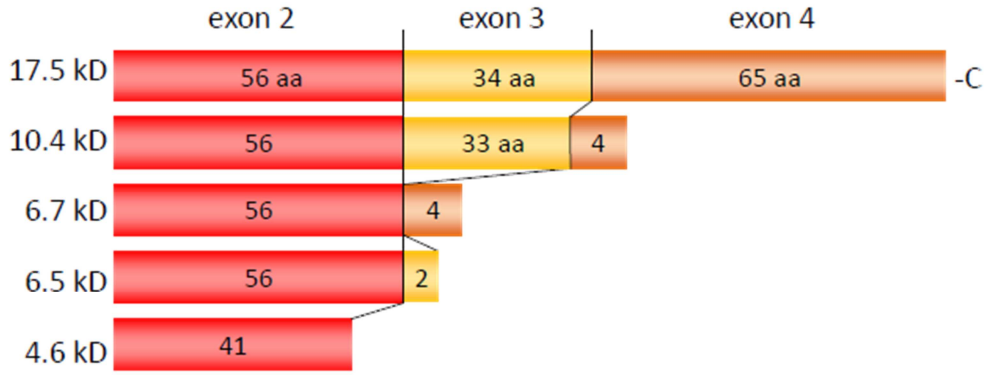

Figure 2. Schematic representation of the human FGF1 isoforms.

The FGF1 gene transcript is basically composed of 4 exons and second to fourth exons are protein-coding.
The transcription is regulated by at least 4 distinct promoters in different upstream untranslated exons, designated 1A, 1B, 1C, and 1D.
These are alternatively spliced to the first protein-coding exon (Chiu et al., 2001). The promoter 1A derived transcript dominantly expresses in the kidney (Myers et al., 1993), 1B in the brain and retina (Myers et al., 1993; Myers et al., 1995), and 1C and 1D in vascular smooth muscle cells and fibroblasts (Chotani et al., 2000).

Protein

Description

FGFs control multiple biological processes such as proliferation, survival, migration and differentiation of a variety of cell types (Lanner and Rossant, 2010; Guillemot and Zimmer, 2011). The human and mouse FGF family consists of 22 members that are expressed in almost all tissues. Among the FGF family, FGF1 and FGF2 are prototypic FGF and have been extensively characterized. They were originally isolated from the brain and pituitary as mitogens for fibroblast cells in vitro (Gospodarowicz, 1975; Itoh and Ornitz, 2011).
FGF1 contains characteristic β-trefoil structure, since FGF1 contains 12 antiparallel β strands which assemble into a pattern with threefold internal symmetry (Zhu et al., 1991, Brych et al., 2001). Key residues responsible for Interaction between FGF1 and heparin or its receptor are characterized by crystal structure (Pellegrini et al., 2000; Mohammadi et al., 2005a; Mohammadi et al., 2005b).
FGF1 is unique among FGFs because of its ability to bind and activate all known FGFRs, FGF1 is considered to be the universal FGFR ligand (Zhang et al., 2006).
Comparison of the crystal structures of FGF1-FGFR1c, FGF1-FGFR2c, and FGF1-FGFR3c complexes has provided key insights into the unique FGFR binding promiscuity of FGF1 (Olsen et al., 2004).

Expression

Although first isolated from brain and pituitary on the basis of their ability to induce fibroblasts proliferation, FGF1 is widely expressed in developing and adult tissues (Gospodarowicz, 1974; Gospodarowicz, 1975; Gospodarowicz et al., 1978; Itoh and Ornitz, 2004). Immunohistochemical staining has shown that colorectal and gastric tissues, both normal and tumor, express FGF1, and the immunoreactivity is mainly cytoplasmic (el-Hariry et al., 1997). Various amounts of FGF1 are detected in hepatocellular carcinoma, whereas it cannot be detected in normal (Chow et al., 1998). FGF1 mRNA is detected in several types of breast epithelial cell lines such as normal (NMEC), transformed (HBL-100) (Renaud et al., 1996) and cancer cell lines MCF7, BT-20, MDA-MB-231 (Penault-Llorca et al., 1995; Renaud et al., 1996), while BT474, T47D and ZR75.1 do not express FGF1 mRNAs (Penault-Llorca et al., 1995).

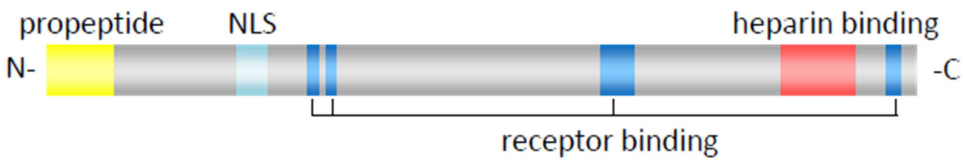

Figure 3. Domaine structure of FGF1. FGF1 contains a nuclear localization signal (NLS) at N-terminal region and heparin binding site is located C-terminal.

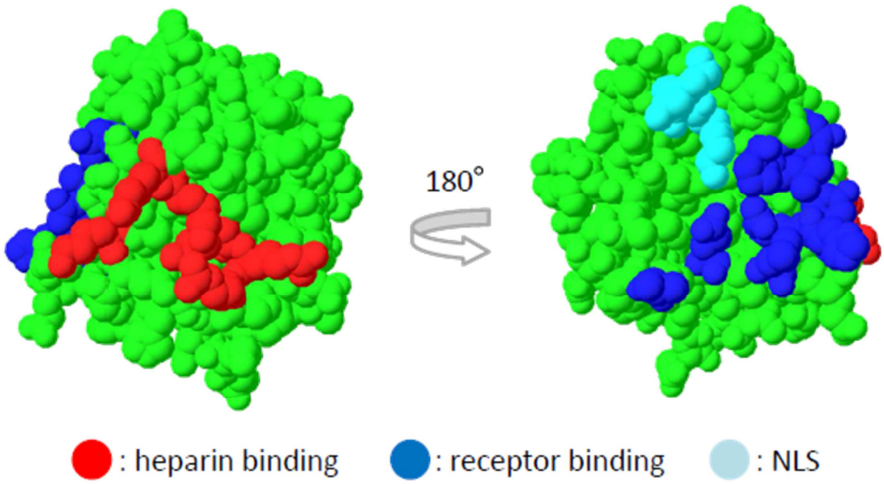

Figure 4. Crystal structure of FGF1. Ternary structures are depicted by its crystal structure and representative residues for the binding to its receptor (blue) and heparin (red) are shown.

Localisation

FGF1 lacks the classical signal sequence, since it employs non-classical pathway to be secreted. FGF1-S100A13-SYT complex formation is required for passing through the cell membrane (Mouta Carreira et al., 1998; Tarantini et al., 1998; Landriscina et al., 2001). Secreted extracellular FGF1 can be internalized following its binding to cell surface receptors by the clathrin-mediated pathway (Wiedlocha and Sørensen, 2004). FGF1 induces FGF receptor translocation from the cell membrane to the nucleus upon interaction with its receptor during the G1 phase of the fibroblast cell cycle (Prudovsky et al., 1994). FGF1 could be enters the nucleus by its putative nuclear localization sequence (NLS) (Imamura et al., 1990; Rodriguez-Enfedaque et al., 2009). Other groups suggest that nuclear translocation of FGF1 is controled not only by NLS, but also an additional sequence which prevents endogenously expressed FGF1 from NLS dependent translocation to the nucleus, and also FGF1 could move to the nucleus by free diffusion because a molecular weight of FGF1 is only 16500 (Zhan et al., 1992; Cao et al., 1993).

Function

FGF1 is a mitogen for numerous different cell types in vitro. FGF1 has been implicated in a range of physiological processes, including development, morphogenesis, wound healing and angiogenesis (Beenken and Mohammadi, 2009). However, FGF1/FGF2 double-knockout mice do not exhibit any of the phenotypic abnormalities. This results suggest that the developmental and physiological roles of FGF1 are highly restricted, even though its functions remain unclear (Miller et al., 2000).
FGF1 binds to integrin αvβ3 (Mori et al., 2008), and the integrin-binding site of FGF1 overlapps with the heparin-binding site (but not identical). The FGF1 mutant that does not bind to αvβ3 (R50E) is dominant-negative (antagonistic), while it still binds to FGFR1 and heparin (Yamaji et al., 2010). FGF1 induces integin-FGF1-FGFR ternary complex, but R50E does not (Yamaji et al., 2010). R50E suppresses angiogenesis and tumorigenesis (Mori et al., 2013).

Homology

Length of FGFs is in the range of 150 to 300 amino acids. The conserved core 120-amino acid have been shown a 30-60% identity (Itoh and Ornitz, 2004; Itoh and Ornitz, 2007).

Implicated in

Gastrointestinal tumor

Note

FGF1 is overexpressed in 42% of colorectal adenomas, 76% of colorectal cancers, and 54% of gastric cancers as compared to the normal mucosal tissues. These results imply that overexpression of FGF1 often arises in a human colorectal and gastric cancers. FGF1 may play a role in the progression of these tumours (el-Hariry et al., 1997). Cancer-associated fibroblasts expressing fibroblast activation protein (FAP) is implicated in the invasive behavior of colorectal cancer. FAP enhances fibroblast cells to produce FGF1 and activates FGFR3 of colon cancer cells in vitro resulted in the increased cell migration and invasion (Henriksson et al., 2011).

Breast cancer

Note

The majority of breast cancer, including cancer adjacent cells expresses active FGF1 protein (Smith et al., 1994); however, mRNA of FGF1 is

expressed higher level in benign neoplastic and hyperplastic tissue than in malignant tissue (Anandappa et al., 1994). Another group demonstrates that the extent and intensity of immunoreactivity of FGF1 in cancer cells is much greater than those of cells from fibroadenoma or mastopathy (Yoshimura et al., 1998). FGF1 is detected in epithelial cells of breast fibroadenomas, and FGFR4 is expressed both in epithelial cells and stromal fibroblasts. These suggest a paracrine/autocrine regulation of epithelial and stromal cells of fibroadenomas through an FGF1-FGFR4 interaction (La Rosa et al., 2001).

Nerve injury

Note

FGF1 is one of neuronotrophic factor and enhances nerve regeneration process (Walter et al., 1993). FGF1 increases the branching number of myelinated axons that regenerate damaged neurons and FGF1 also induces the axon elongation of primary sensory and motor neurons through the nerve guide in animals (Cordeiro et al., 1989). Protein expression profiles throughout 28 days of peripheral nerve regeneration reveals that FGF1 increases throughout the experimental period in the both proximal and distal nerve segments (Bryan et al., 2012).

Cardiac ischemia

Note

Level of FGF1 in pericardial fluid is associated with severe myocardial ischemia. FGF1 is released from the myocardial tissue into pericardial result from the myocardial ischemia (Iwakura et al., 2000). FGF1 may contribute to the functional preservation for the myocardium damage. In fact, treatment with FGF1 by extravascular delivery system increases coronary flow in the artificially constricted territory (Lopez et al., 1998), and also systemic bolus of FGF1 immediately after myocardial ischemia reduces apoptosis in animal model (Cuevas et al., 1997).

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