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Gene Section
Short Communication

FIGF (c-fos induced growth factor (vascular endothelial growth factor D))

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Identity

Other names: VEGF-D, VEGFD

HGNC (Hugo): FIGF

Location: Xp22.2

DNA/RNA

Description

The VEGFD gene consists of 7 exons and spans 38865 bases on chromosome X in minus strand orientation. The upstream promoter sequence does not contain a canonical TATA box.
The promoter sequence contains an optimal AP-1 binding site at position -54 from the start site.

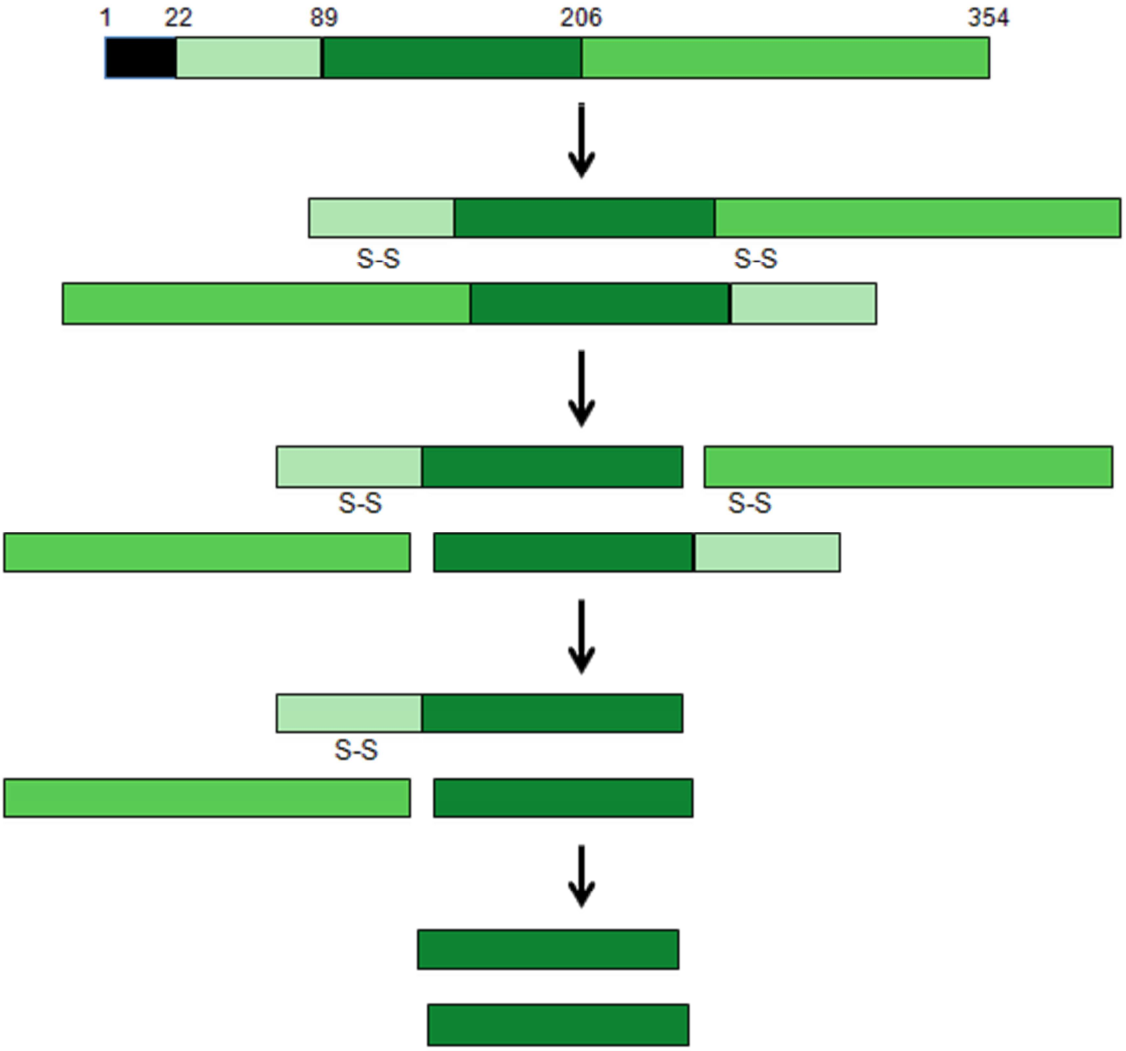
Transcription

The mRNA transcribed from this gene is 2110 nucleotides long.

Protein

Description

VEGF-D is a member of the Platelet-Derived Growth Factor/Vascular Endothelial Growth Factor (PDGF/VEGF) family that contains a conserved domain of eight cysteine residues forming the typical cystine-knot structure involved in the formation of the biologically active dimer (Debinski et al., 2001; Rocchigiani et al., 1998; Yamada et al., 1997; Joukov et al., 1996).
The human VEGF family consists of 5 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D and Placental Growth Factor (PlGF) which differ in their ability to bind to VEGF receptors that are primarily expressed in endothelial cells: VEGFR1 (Flt1), VEGFR2 (KDR, Flk1), VEGFR3 (Flt4), neuropilin-1 and neuropilin-2. VEGFA binds to VEGFR1, VEGFR2, as well as neuropilin-1 and neuropilin-2, whereas PlGF and VEGFB bind only to VEGFR1 and neuropilin-1.
VEGF-C and VEGF-D, which share 23% amino acid sequence identity, are uniquely expressed as preproproteins that contain long N- and C-terminal propeptide extensions around the VEGF homology domain (VHD).
The C-terminal amino acid sequenze show a pattern of spacing cysteine residues reminescent of the BR3P sequence.



The VEGF-D chain is a secreted protein synthesised as 354 amino acid precursor containing a signal peptide (AA:1-21), an N-propeptide (AA:22-88), a VHD (VEGF Homology Domain, AA:89-205) and a C-propeptide (AA:206-354).

Proteolytic processing of the 354 aa VEGF-D preproprotein creates a secreted proprotein. Further processing by extracellular serine proteases, such as plasmin or furin-like proprotein convertases, forms mature VEGF-D consisting of non-covalently linked homodimers of the 117 aa VHD (Stacker et al., 1999; McColl et al., 2003; McColl et al., 2007). Human VEGF-D is ligand for VEGFR-2 and VEGFR-3.

VEGF-D is expressed in fibroblasts and its messenger is stabilized by cell contacts (Orlandini and Oliviero, 2001).

Its receptor VEGFR3 is constitutively expressed in lymphatic endothelial cells and in vascular endothelial cells during angiogenesis and in endothelial precursors and in osteoblasts (Tammela et al., 2011; Orlandini et al., 2006).

VEGF-D and VEGFR-3 are expressed in the osteoblasts of the growing plate.

The treatment of primary human osteoblasts with recombinant VEGF-D induces the expression of osteocalcin and the formation of mineralized nodules in a dose-dependent manner (Orlandini et al., 2006).

Expression

It is expressed in adult lung, heart, muscle, and small intestine, and is most abundantly expressed in fetal lungs and skin.

VEGF-D expression in mouse fibroblasts is induced by cell interaction mediated by cadherin 11 (Orlandini et al., 2006; Avantaggiato et al., 1998).

Localisation

Secreted in the extracellular medium.

Function

Growth factor active in angiogenesis, lymphangiogenesis and endothelial cell growth, stimulating their proliferation and migration of blood cells. It may function in the formation of the venous and lymphatic vascular systems during embryogenesis, and also in the maintenance of differentiated lymphatic

endothelium in adults. Binds and activates VEGFR-2 (Flk1) and VEGFR-3 (Flt4) receptors.
VEGFD controls the total length and complexity of dendrites both in cultured hippocampal neurons and in the adult mouse hippocampus (Mauceri et al., 2011).
VEGFD together with SDF1α and sFRP1 are major components of stromal cell-derived inducing activity of dopaminergic neurons (Schwartz et al., 2012).

Homology

VEGF-D is highly conserved, it shares 94%, 95%, 99%, 97% and 93% aa identity with mouse, rat, equine, canine and bovine VEGF-D, respectively.

Mutations

Note
Single Nucleotide Polymorphism have been described in mRNA UTR, introns or in exons: see NCBI database.

Implicated in

Lymphangioleiomyomatosis

Note
VEGF-D prognostic marker for tumor growth and dissemination.

Disease
High level VEGFD in patients with lymphangioleiomyomatosis.

Prognosis
Serum VEGF-D may be a clinically useful diagnostic test that can distinguish sporadic lymphangioleiomyomatosis from other cystic and chylous lung diseases, potentially decreasing the need for lung biopsy (Young et al., 2008).

Metastasis

Note
VEGF-D-dependent regulation of the prostaglandin pathway induces lymphatic vessel dilation and subsequent increase of metastatic spread (Karnezis et al., 2012).

Soft tissue sarcoma

Note
VEGF-D significantly increases the migration of sarcoma cells through lymphatic endothelial monolayers. The VEGF-D-dependent induced migration through lymphatics might be the reason for relationship between VEGF-D expression and lymph node metastasis in soft tissue sarcomas (Yanagawa et al., 2012).

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