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Gene Section
Review

EDIL3 (EGF-Like Repeats And Discoidin I-Like Domains 3)

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Abstract

Review on EDIL3, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: DEL1

HGNC (Hugo): EDIL3

Location: 5q14.3

Note

EDIL3 is developmentally regulated and expressed during embryogenesis. It is expressed in extraembryonic mesoderm, specifically the yolk sac blood islands. EDIL3 is detected in angioblasts and early endothelial cells in four developing organs: heart, lung, kidney, and eye. It is also expressed in hypertrophic chondrocytes. Additionally, EDIL3 has a function that affects endocytosis, apoptosis, cell migration, or some combination thereof.

DNA/RNA

Note

EDIL3 is an extracellular matrix protein that contains three EGF-like repeats and two discoidin I-like domains. The second EGF-like repeat contains an RGD integrin binding motif that appears to be a ligand for alpha-v beta-3 integrin receptor.

Similarly, EDIL3 shares consensus sequences with the fate determining notch proteins and coagulation factor IX, coagulation factor V, and coagulation factor VIII.

Description

442.48 kb, mRNA: 2974 bp, 11 Exons.

Transcription

The major transcript is represented by the most common cDNA clones, and it encodes a 480 amino acid protein in human. The major transcript encodes a protein that consists of a signal peptide comprising three epidermal growth factor- (EGF)-like repeats and two discoidin I-like domains. A less frequently represented minor transcript designated the minor transcript encodes a signal peptide comprising three EGF repeats and a portion of the amino-terminal discoidin I-like domain. There is additional complexity among other minor transcripts; specifically, the variation is in the inclusion or exclusion of sequences that encode 10 amino acids in the spacer region between EGF1 and EGF2.

Pseudogene

Not known.

Protein

Note
EDIL3 contains three Ca-binding EGF-like repeats and two discoidin I-like domains. There is an integrin-binding site in the second EGF-like repeat; specifically, this EGF-like repeat has an RGD peptide that binds to integrin alpha v beta 3.

Description

EDIL3 has 480 amino acids, and its molecular weight is 52 kDa protein.
EDIL3 comprises 480 amino acids, and its molecular weight is 52 kDa protein.
- The domain of 1-23 is an initio prediction. The subsequent domain is 24-470 which EGF-like repeat and discoidin I-like domain-containing protein 3 isoform 2.
The region name is EGF1 which Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular proteins.
- Location: 27-59; many of these proteins require calcium for their biological function and calcium-binding sites.
The region name is EGF2 which Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular proteins.
- Location: 69-107; Many of these proteins require calcium for their biological function and calcium-binding sites.
The region name is EGF3 which Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular proteins.
- Location: 109-145; many of these proteins require calcium for their biological function and calcium-binding sites.
- Location: 109112126; Ca2+ binding site.
The region (147-304) name is FA58C which note - Coagulation factor 5/8 C-terminal domain, discoidin domain.
The region name is FA58C which note - Coagulation factor 5/8 C-terminal domain, discoidin domain; Cell surface-attached carbohydrate-binding domain, present in eukaryotes and assumed to have horizontally transferred to eubacterial genomes (150-303), sugar binding site (196224231).
The region (308-466) name is FA58C which note - Coagulation factor 5/8 C-terminal domain, discoidin domain.
The region name is FA58C which note - Coagulation factor 5/8 C-terminal domain, discoidin domain; Cell surface-attached carbohydrate-binding domain, present in eukaryotes and assumed to have horizontally transferred to eubacterial genomes (311-465), sugar binding site (358386393).

Expression

EDIL3 is differentially expressed depending on the tissue and cell culture conditions.
Organism parts: (see below).
Kidney, myometrium, bone, spinal cord, stomach fundus, heart, colon cecum, urethra, islet of Langerhans, synovial membrane, lung, atherosclerotic aortic wall, internal mammary artery, liver tumor tissue, accumbens, amygdale, brain, caudate nucleus, central nervous system, cerebral cortex, colon mucosa, corpus callosum, dorsal root ganglion, frontal cortex, primary motor cortex, Brodmann's Area 4, frontal lobe, hippocampus, hypothalamus, medulla, midbrain, nodose nucleus, homogenized, occipital lobe, parietal lobe, putamen, saphenous vein, skin, substantia nigra, subthalamic nucleus, temporal lobe, testis, thalamus, trigeminal ganglion, umbilical cord, ventral tegmental area, vestibular nuclei superior, cervix, ovary, stomach, liver, smooth muscle.
The above data derive from the EDIL3 entry in the Expression Atlas.
Diseases: (see below)
Breast carcinoma, sarcoma, Combined Hepatocellular Cholangiocarcinoma (CHC), Intrahepatic Cholangiocarcinoma (ICC), leiomyosarcoma, pituitary cancer, extranodal NK/T-cell lymphoma, osteosarcoma, undifferentiated sarcoma, invasive ductal carcinoma, mucosa-associated lymphoid tissue lymphoma, papillary thyroid carcinoma, peripheral T-cell lymphoma, pancreatic cancer, cervical cancer, clear cell renal carcinoma, engineered invasive esophageal squamous cell carcinoma, prostate carcinoma.
The above data derive from the EDIL3 entry in the Expression Atlas.
Cell lines: (see below)
DU145, ACHN, CaOv3, Caki2, H460, HeLa, KG1, MDAMB231, GM10833, GM13883, HCC70, U87 CuFi, U251, NCIH1623, SCC-25, 786-O, ITM, HCC-1428, HuNS1, AG10750, LNCAP, SW780, AG11498, KTCL26, NCIH1436, Capan2, GM10842, HMESO, SKRC54, UMRC3, 639V, A172, A7, Acute Lymphoblastic Leukemia cell line SEM-K2, BE2C, BHT101, BM1604, C32TG, C4II, CCFSTTG1, CESS, CGTHW1, CHP212, COLO320DM, COLO320HSR, COLO704, CORL279, CORL88, Calu1, D283Med, DBTRG05MG, DKMG, DMS114, DMS273, Detroit562, GDM1, GLI60 glioblastoma cell line, H1975, H4, H460a, HCC1143, HCC1395, HDMYZ, HOS, HT1080, HT3, HuPT4, IM9, KHOS240S, KU812, L591, MCF-7/LTED,,MCF10-T1k (MII), MDA-MB-231, MT4, NCIH1048, NCIH1355, NCIH1395, NCIH1563,

NCIH1651, NCIH1694, NCIH1770, CIH1792, NCIH1975,NCIH1993, NCIH2009, NCIH2030 ,NCIH2052, NCIH2228, NCIH226, NCIH2347, NCIH358, NCIH446, NCIH524, NCIH69, NCIH716, NCIH748, NCIH810, NCIH82, OE21, PC-3, PC-3/Mc, RCC4, RDES, SCaBER, SHP77, SJRH30, SJSA1, SKLMS1, SKMES1, SKNEP1, SNB19, SNU18, 2SNU387, SNU423, SNU449, SNU475, SW1088, SW1353, SW1783, SW1990, SW756, SW900, SW954, SW982, T98G glioma, TaY-E10, UT-15, WI38, WM115, Y79, YPAC, A498, BT474, PC3, SKOV3, HL-60, A549.
The above data derive from the EDIL3 entry in the Expression Atlas Expression Atlas.

Function

EDIL3 promotes adhesion of endothelial cells to extracellular matrix through interaction with the alpha-v/beta-3 integrin receptor. It inhibits the formation of vascular-like structures in vitro. Exogenous EDIL3 causes abnormal vasculature in chick embryos. Overexpression of EDIL3 decreases vasculature in mesenteric vessels. It may be involved in the regulation of vascular morphogenesis and remodeling during embryonic development.
Reportedly, high expression of EDIL3 by cancer cells is an indicator of poor prognosis, possibly because EDIL3 can enhance vascular formation in hepatocellular carcinoma, colon cancer, and experimental models with an osteosarcoma cell line or with Lewis lung carcinoma. However, an EDIL3 fragment containing the third EGF-like repeat induces apoptosis. In a mouse model of cancer involving an explanted tumor, gene therapy with DNA encoding a recombinant protein comprising the third EGF-like repeat and the first discoidin 1 like domain efficiently induces apoptosis, reduces tumor growth, and improves prognosis.

Homology

The EGF repeats of EDIL3 are homologous to molecules such as Notch (Accession: NM_017617.3) and its ligands Crumbs (Accession: CH471090.1) and Delta (Accession: NT_033777.2). There is also considerable homology in this region to the following four other proteins: a developmental sea urchin protein fibropellin (Accession: NW_003578619.1); a factor shown to function in lineage commitment of adipocytes (Accession: NC_000003.11); an endothelial cell-specific receptor tyrosine kinase (Accession: NC_000070.6) known to be essential for embryonic blood vessel development; and coagulation factor IX (Accession: NM_000133), which has a role in the coagulation cascade. In its discoidin I-like domains, EDIL3 is homologous to five proteins: the mammary epithelial cell marker milk fat globule membrane protein (Accession: NC_000015.9), coagulation factors V (Accession: NC_000001.10) and VIII (Accession: NP_000123.1), the extracellular domain of a group of tumor-associated orphan receptor tyrosine kinases (Accession: Q01973, Q01974), and discoidin domain receptor tylosin kinase (Accession: AB_202100, BC_052998).

Mutations

Note
Not known in human.

Implicated in

Hepatocellular carcinoma (HCC)

Note
When immunocytochemistry and tumor tissue samples from 101 patients with HCC were used to examine expression level of EDIL3 protein in HCCs, EDIL3 was detected in the cytoplasm of HCC cells. Overall, 95 (94.06%) of the 101 patients exhibited EDIL3-positive expression in the respective HCC samples, and 6 (5.94%) exhibited EDIL3-negative expression in the HCC samples. Among these 101 patients with HCC, 49 (48.5%) exhibited high levels of EDIL3 expression in normal somatic tissue, and 52 (51.5%) exhibited low levels of EDIL3 expression. The high expression level of EDIL3 protein in HCC samples was a significant prognostic factor for poor overall survival among patients with HCC. The 5-year survival rate among patients with HCC and a high or a low EDIL3 protein expression level was 32.4% and 53.2%, respectively. (Sun et al., 2010).

Colon cancer

Note
Tumor tissues from 10 patients with colon cancer were immunostained with anti-Del1 antibody, and Del1 was found to be expressed in each colon cancer tissue sample (100%) at various levels. Using a mouse model of colon cancer involving explanted cells from a culture line, both Del1-shRNA and VEGF-shRNA gene therapies showed a synergic effect in suppressing growth of explanted tumors by anti-angiogenesis and anti-proliferation. (Zou et al., 2009).

Other tumors

Note
In cases of basal cell carcinoma or astrocytoma, Del1 expression was detected via immunohistochemistry, and Del1 expression was primarily evident in the matrix and basement membrane that surrounded tumor cells. Low-level Del1 staining was also evident over some of the cell bodies. Del1 signal was not detected in tumor-associated endothelial cells.

A large percentage of cells in primary breast carcinomas, melanomas, and colon cancers in humans reportedly express Del1. Additionally, endothelial cells also reportedly express Del1 in these tumors.
Aoka et al. have reported that Del1 accelerates tumor growth by enhancing vascular formation in a mouse explanted tumor model involving an osteosarcoma cell line (Aoka et al., 2002).

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