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Gene Section
Review

TIE1 (tyrosine kinase with immunoglobulin-like and EGF-like domains 1)

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Identity

Other names: JTK14, TIE

HGNC (Hugo): TIE1

Location: 1p34.2

Note

Receptor tyrosine kinase, member of the TIE family (other member: TIE2/TEK). Highly conserved sequence across vertebrate species, with greatest amino acid homology occurring in the kinase domain.

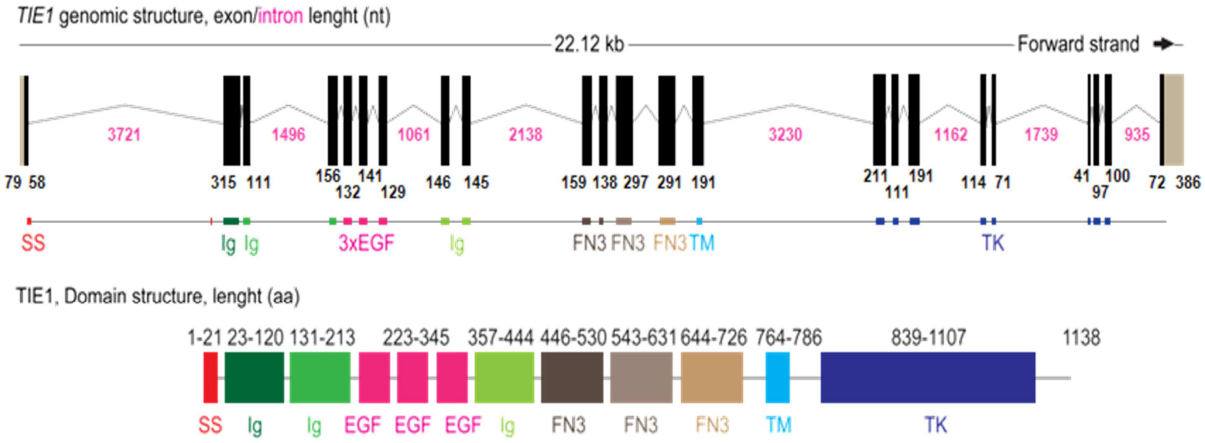
DNA/RNA

Description

The human TIE1 gene spans 22115 bp, encoding for 23 exons in forward strand.

Transcription

Longest mRNA contains 3882 bp. Alternatively spliced forms have been reported, including transcript variant 5 (EU826590.1) coding for a soluble TIE1 ectodomain (Jin et al., 2008).



The genomic (top) and the protein domain structures (below) of human TIE1. Black boxes represent exons with intervening intron sequences (lines), light gray boxes represent non-coding sequences of first and last exons. Exon length (black text) and intron length of the longest introns (pink) are indicated in nucleotides. The protein domain coding regions of exons are indicated with colours according to the TIE1 protein domain structure. SS= signal sequence, Ig= immunoglobulin-like domain, EGF= epidermal growth factor-like domain, FN3= fibronectin type-III domain, TM= transmembrane domain, TK= tyrosine kinase domain. Protein domain prediction was performed using (SMART). The crystal structure for Tie2 shows the existence of a third Ig-like domain, immediately after the SS (Barton et al., 2006), and homology modeling of Tie1 predicts a similar fold (Seegar et al., 2010).

Protein

Note
See figure above.

Description

Human TIE1 contains 1138 aa. It belongs to the protein kinase superfamily, protein receptor tyrosine kinase family, TIE subfamily.
It contains 3 Ig (immunoglobulin)-like domains (I set type), 3 EGF (epidermal growth factor)-like domains, 3 fibronectin type-III domains, a single transmembrane domain and 1 intracellular split tyrosine kinase domain (Partanen et al., 1992).

Expression

TIE1 is almost exclusively expressed in endothelial cells both in human and in mouse. High expression of TIE1 mRNA is found in adult lung, heart, and placenta, some expression in kidney, whereas muscle, brain, liver and pancreas contain less TIE1 mRNA.
Tie1 mRNA is present widely in fetal tissues starting at embryonic day 8,5 (Korhonen et al., 1992).
Tie1 mRNA is detected in differentiating angioblasts of the head mesenchyme, in the splanchnopleure and dorsal aorta as well as in migrating endothelial cells of the developing heart, in the heart endocardium and in the endothelial cells forming the lung vasculature (Korhonen et al., 1992).
TIE1 is also expressed on cultured endothelial cells, some haemopoietic progenitor cells, some myeloid leukemia cell lines having erythroid and megakaryoblastoid characteristics (Batard et al., 1996) and in adult acute myelogenous leukemia (Kivivuori et al., 2007).
TIE1 expression is increased in angiogenic endothelial cells during wound-healing, in proliferating ovarial capillaries during hormone-induced superovulation and in tumor blood vessels (Korhonen et al., 1992; Kaipainen et al., 1994). Tie1 is downregulated in endothelial cells by shear stress (Chen-Konak et al., 2003), but specifically induced in the mouse vasculature by disturbed flow in vascular bifurcations and branching points along the arteries (Porat et al., 2004).
TIE1 along with ANGPT2 and TEK mRNAs were strongly expressed in cells of Kaposi's sarcoma tumor cells, and cutaneous angiosarcomas, in contrast to the focal low-level expression in normal skin biopsies (Brown et al., 2000).

Localisation

Cell membrane.

Function

Studies of Tie1 gene targeted mice have revealed that Tie1 is critical for the development of blood (Puri et al., 1995) and lymphatic vasculatures (D'Amico et al., 2010; Qu et al., 2010) after midgestation.
Tie1 is essential for endothelial cell survival in the developing microvasculature undergoing angiogenic sprouting, and essentially in all blood vessels in adult (Partanen et al., 1996). $Tie1^{-/-}$ embryos die around embryonic day 13,5, depending on the background (Puri et al., 1995; D'Amico et al., 2010). The Tie1 deficient or hypomorphic embryos show also signs of edema, due to lymphatic defects involving abnormally patterned lymph sacs and peripheral lymphatic vessels (D'Amico et al., 2010; Qu et al., 2010).
The molecular function of TIE1 is not completely understood, as it does not directly bind the angiopoietin growth factors, which are the ligands for TEK (TIE2). However, TIE1 tyrosine phosphorylation is induced by angiopoietin-1 (Saharinen et al., 2005; Yuan et al., 2007), most likely in a complex with TEK (Marron et al., 2000; Saharinen et al., 2005). Angiopoietins activate TEK in a unique manner, which involves the translocation of TEK to endothelial cell-cell contacts, and TIE1 is also present in these complexes (Saharinen et al., 2008). Activation of the TIE1 kinase activity using chimeric TIE1 receptors was found to result in the activation of the Akt pathway (Kontos et al., 2002). The TIE1 ectodomain is proteolytically cleaved, and the cleavage is enhanced by PMA, VEGF and TNF-α (Yabkowitz et al., 1999). The proteolytic processing of TIE1 may regulate TEK activity (Marron et al., 2007).
The deletion of both Tie1 and Tek results in a more severe phenotype than the deletions of either Tie1 or Tek alone (Sato et al., 1995; Puri et al., 1999). The deletion of both Tie1 and Angpt1 resulted in impaired development of the right-hand, but not left-hand side venous system in the mouse embryo (Loughna and Sato, 2001). TIE1 has been implicated as a proinflammatory gene and its silencing in cultured endothelial cells reduced the expression of proinflammatory genes (Chan and Sukhatme, 2009), while TIE1 overexpression upregulated adhesion molecules including VCAM-1, E-selectin and ICAM-1 (Chan et al., 2008).

Homology

H. sapiens: TIE1; M. musculus: Tie1; R. novergicus: Tie1; D. rerio: tie1; X. tropicalis: tie1.

Mutations

Somatic

Somatic missense mutations and synonymous substitutions in TIE1 have been detected in human cancers, but their significance remains to be found out.

Implicated in

Various diseases

Note
TIE1 has not been directly shown to be involved in any human diseases. Most of the information concerning Tie1 function has been retrieved from animal models.

Gastric cancer

Note

TIE1 expression has been detected in gastric adenocarcinoma tissues where its expression inversely correlated with patients' survival (Lin et al., 1999).

Atherosclerosis

Note

Tie1 is upregulated in emerging atherosclerotic plaques and around developing aneurysms (Porat et al., 2004), and $Tie1^{+/-}$ mice bred to the ApoE-deficient background displayed a 35% reduction in atherosclerosis relative to $Tie1^{+/+}$;$Apoe^{-/-}$ mice (Woo et al., 2011).

To be noted

Note

Recently, ANGPT2, a ligand for TEK, has been identified as a promising target for novel anti-angiogenic tumor therapies, and inhibition of ANGPT2 has resulted in inhibition of tumor growth, angiogenesis, lymphangiogenesis and metastasis in preclinical models (Oliner et al., 2004; Brown et al., 2010; Mazzieri et al., 2011; Holopainen et al., 2012). In a phase II clinical trial ANGPT1/ANGPT2 dual blocking peptibodies in combination with paclitaxel prolonged the progression-free survival of the ovarian cancer patients (Karlan et al., 2012). In addition, the adenoviral delivery of anti-Tek intrabodies impaired tumor growth in preclinical models (Popkov et al., 2005). ANGPT1 appears to mediate vascular normalization of the tumor blood vessels during VEGF or ANGPT2 blocking anti-angiogenic therapy (Winkler et al., 2004; Falcón et al., 2009). Although evidence for the function of TIE1 in tumors is lacking, it should be noted that via interaction with TEK, TIE1 might be involved in tumor angiogenesis and progression.

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