Gene Section

Review

**TNFSF15 (tumor necrosis factor (ligand) superfamily, member 15)**

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### Identity

**Other names:** MGC129934; MGC129935; TL1; TL1A; VEGI; VEGI192A

**HGNC (Hugo):** TNFSF15

**Location:** 9q32

**Local order:** TNFSF15 gene at 9q32, near the CD30L gene at 9q33.

### DNA/RNA

#### Description

The human VEGI gene spans about 17 kb and consists of four exons.

#### Transcription

The size of VEGI mRNA is approximately 6.5 kb.

Boxes with roman numerals above represent exons and horizontal lines represent intronic sequence. The putative transcription start site is indicated by a double arrowhead. R denotes the 5’ untranslated sequence unique to each respective transcript, and stippled box represents the common 3’ untranslated region.

Figure A. All three isoforms.
It is unusual for a human gene of 6.5 kb to contain only a small open reading frame of 522 nucleotides. Multiple VEGI transcripts generated by the use of cryptic splice sites and alternate exons.

**Pseudogene**
Not known.

**Protein**

**Description**
Hydrophobicity analysis of VEGI predicts a 13 amino acid hydrophobic region that follows the amino terminal segment of 12 amino acids, suggesting a structure characteristic of a type II transmembrane protein, with residues 26-174 constituting an extracellular domain analogous to domains found in other TNF family members. VEGI isoforms exhibit a carboxyl terminal domain of 151 amino acid residues, which is encoded by part of the fourth exon, termed IVb. The initially characterized VEGI isoform, designated VEGI-174, is encoded by the fourth exon (parts IVa and IVb) alone, which includes both the putative transmembrane domain and the conserved extracellular domain. There are two additional endothelial-specific transcripts of 7.5 and 2.0 kb, which encode peptides of 251 (VEGI-251) and 192 (VEGI-192) residues, respectively. The VEGI-251 and -192 isoforms differ in their amino terminal regions, but share the conserved 151-amino acid residue carboxy terminal domain. VEGI-251 possesses a putative secretory signal peptide and its overexpression causes apoptosis of endothelial cells and inhibition of tumor growth.

**Expression**
VEGI is specifically expressed in endothelial cells. Analysis of total RNA preparations from many cell lines and primary cell cultures by Northern blot analysis confirmed the specificity of VEGI expression, with only HUVEC and human venous endothelial cells demonstrating detectable levels of expression. Using multiple tissue Northern blots, the VEGI transcript was found in many adult human tissues, including placenta, lung, skeletal muscle, kidney, pancreas, spleen, prostate, small intestine, and colon, suggesting that the gene product may play a role in the function of a normal vasculature. The failure to detect the transcripts of this new gene in some of the human tissues probably is due to relatively small proportion of endothelial cells in these tissues. Using isoform-specific probes, we have determined that the distribution profiles of VEGI isoforms in human organs and tissues appear to be different. The 7.5 kb transcript encoding VEGI-251 was expressed at high levels in the placenta, kidney, lung and liver, whereas the 2 kb transcript corresponding to VEGI-174 was observed in liver, kidney, skeletal muscle and heart. VEGI-174 mRNA was more abundant in heart, skeletal muscle, pancreas, adrenal gland, and liver, while VEGI-251 was more abundant in fetal kidney and fetal lung. Overlapping expression of VEGI-251 and VEGI-174 mRNA was detected in prostate, salivary gland and placenta, whereas VEGI-192 mRNA was not readily detected by Northern blot. These expression patterns suggest the possibility of tissue or developmentally specific functions for VEGI isoforms.
Alternatively, this expression pattern also supports the view that one VEGI isoform is the functional cytokine, while the others act in regulatory roles to modulate the activity of the active isoform. In this case, it is possible that the non-functional isoforms do not exist at the protein level. VEGI isoform expression has also been examined in cultured cells by RNase protection assay. All three known VEGI isoforms were detected in human endothelial cells, including coronary artery endothelial (HCAE), HUVE cells, and human microvascular endothelial (HMVE) cells. Very low levels are sometimes detected in adult bovine aortic endothelial (ABAE) cells. Little VEGI expression was detectable in human coronary artery smooth muscle (CASM) and mouse endothelioma bEND.3 cells. More than one isoform is detectable simultaneously, with VEGI-251 being the most abundant. The expression of this protein is inducible by TNF and IL-1 alpha, but not by gamma-interferon.

**Localisation**

Endothelial cells and monocytes. However, VEGI was not expressed in either B or T cells.

**Function**

VEGI is an endogenous inhibitor of angiogenesis produced largely by vascular endothelial cells and exerts a specific inhibitory activity on the proliferation of endothelial cells. VEGI enforces growth arrest of endothelial cells in G0 and early G1 phases of the cell cycle but induces apoptosis in proliferating endothelial cells. The MAPKs p38 and jun N-terminal kinase (JNK) are required for VEGI-mediated endothelial inhibition. Engineered overexpression of secreted VEGI by cancer cells or systemic administration of recombinant VEGI to tumor-bearing mice inhibits tumor growth in numerous tumor models. Recent studies show that VEGI helps modulate the immune system by activating T cells and stimulating dendritic cell maturation, suggesting that VEGI is directly involved in modulating the interaction between the endothelium and the immune system. Recombinant VEGI has an inhibitory activity on mouse bone marrow-derived EPCs in culture, preventing their differentiation toward endothelial cells. Interaction of TL1A with DR3 promotes T cell expansion during an immune response (Migone et al., 2002).

**Homology**

VEGI exhibits 20-30% sequence homology to human TNF-alpha, TNF-beta, and the Fas ligand, similar to that among other TNF family members.

**Implicated in**

**Colon carcinoma**

**Note**

Local production of a secreted form of VEGI via gene transfer caused complete suppression of the growth of MC-38 murine colon cancers in syngeneic C57BL/6 mice. Histological examination showed marked reduction of vascularization in MC-38 tumors that expressed soluble but not membrane-bound VEGI or were transfected with control vector. The conditioned media from soluble VEGI-expressing cells showed marked inhibitory effect on in vitro proliferation of adult bovine aortic endothelial cells.
**Breast cancer**

**Note**
The anticancer potential of VEGI was examined in a breast cancer xenograft tumor model in which the cancer cells were co-injected with Chinese hamster ovary cells overexpressing a secreted form of the protein. The co-injection resulted in potent inhibition of xenograft tumor growth. Our findings are consistent with the view that VEGI is an endothelial cell-specific negative regulator of angiogenesis.

**Mucosal vaccine adjuvant**

**Note**
Kayamuro et al., (2009) reported that TL1A induced the strongest immune response and augmented OVA-specific IgG and IgA responses in serum and mucosal compartments, respectively. The OVA-specific immune response of TL1A was characterized by high levels of serum IgG1 and increased production of IL-4 and IL-5 from splenocytes of immunized mice, suggesting that TL1A might induce Th2-type responses. These findings indicate that TL1A has the most potential as a mucosal adjuvant among the TNFS superfamily genes and their constitutive and inducible expression in hematopoietic and non-hematopoietic cells. Gene. 1997 Dec 19;204(1-2):35-46

**Inflammatory bowel disease**

**Note**
Bamias et al., (2003) provided evidence that the novel cytokine TL1A may play an important role in a Th1-mediated disease such as Crohn’s disease. Takedatsu et al., (2008) revealed that TL1A is an important modulator in the development of chronic mucosal inflammation by enhancing T(H)1 and T(H)17 effector functions. The central role of TL1A represents an attractive, novel therapeutic target for the treatment of Crohn’s disease patients.

**Inflammatory arthritis**

**Note**
Bull et al., (2008) demonstrated that the DR3-TL1A pathway regulates joint destruction in two murine models of arthritis and represents a potential novel target for therapeutic intervention in inflammatory joint disease. Bamias et al., (2008) concluded that TL1A may serve as an inflammatory marker in rheumatoid arthritis. Interactions between TL1A and its receptors may be important in the pathogenesis of rheumatoid arthritis.

**Renal inflammation and injury**

**Note**
Al-Lamki et al., (2008) suggested that TL1A may contribute to renal inflammation and injury through DR3-mediated activation of NF-kappaB and caspase-3, respectively, but that an unidentified receptor may mediate the NF-kappaB-independent induction of TNFR2 in tubular epithelial cells.

**References**


TNFSF15 (tumor necrosis factor (ligand) superfamily, member 15) Yang GL, et al.


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