

# Gene Section

## Mini Review

# THBS1 (thrombospondin-1)

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## Identity

**Other names:** TSP1; platelet glycoprotein G

**HGNC (Hugo):** THBS1

**Location:** 15q15

**Local order:** Telomeric to FLJ39531, centromeric to FSIP1 (fibrous sheath interacting protein 1)

## DNA/RNA

### Description

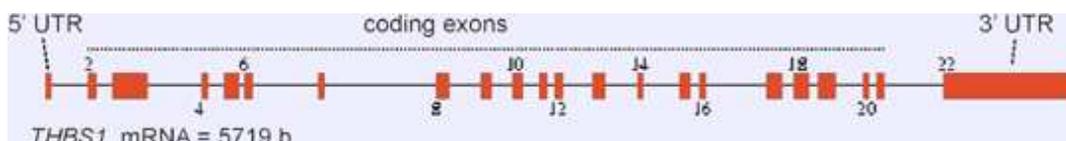
The THBS1 gene is 16,393 bases in size and is composed of 22 exons. Exons 2-21 encode the 5729 b mRNA.

### Transcription

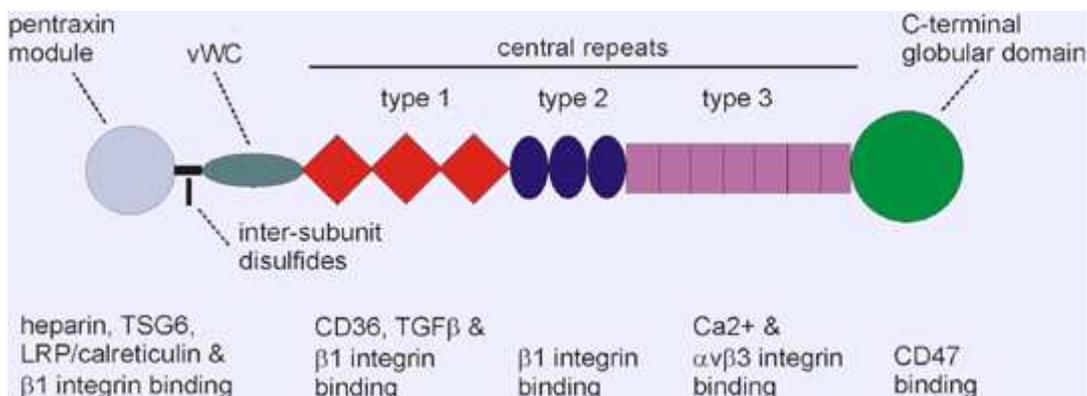
Egr-1 and Sp1 sites function in the constitutive transcription of THBS1 stimulated by serum. Transcription is regulated by c-Jun/AP-1 in cooperation with the repressor Yin Yang-1 (YY-1) and by p53. USF2 mediates glucose-induced TSP1 transcription. Id1 represses transcription. The ATF-1 transcription factor also down-regulates transcription of TSP1 through an ATF/cAMP-responsive element-binding protein binding site. In contrast, Myc increases turnover of thrombospondin-1 mRNA. Transcription of THBS1 in some human cancers is suppressed through hypermethylation.

### Pseudogene

None described.



Intron-exon organization of the THBS1 gene.



Domain organization and localization of selected ligand binding sites in TSP1. TSP1 is a homotrimer linked via disulfide bonds.

## Protein

### Description

The TSP1 precursor contains 1170 amino acids; 129,412 Da. The mature secreted protein comprises residues 19-1170 and assembles into a disulfide linked homotrimer. Secreted TSP1 is a glycoprotein with a molecular mass of 150-180 kDa that contains approximately 12 Asn-linked mono-, bi- tri-, and tetraantennary complex oligosaccharides and variable numbers of C-mannosylated Trp residues in the type 1 repeats.

### Expression

TSP1 is expressed in many tissues during embryonic development but has limited expression in the healthy adult. TSP1 is the most abundant protein in alpha granules of platelets, but normal plasma levels are very low (typically 100-200 ng/ml). Expression in other cell types is induced by wounding, during tissue remodeling, in atherosclerotic lesions, rheumatoid synovium, glomerulonephritis, and in stroma of many tumors. Conversely, most but not all malignant cells in tumors exhibit loss of TSP1 expression during malignant progression. This loss is due to diminished positive regulation of the THBS1 gene by suppressor genes such as p53 and NM23 and increased negative regulation by oncogenes including Ras and Myc. TSP1 expression is induced by TGF-beta, vitamin A, progesterone, and retinoids and suppressed by nickel, Id1, and hepatocyte growth factor. TSP1 expression in the epidermis of skin is suppressed following exposure to UV irradiation.

### Localisation

TSP1 is secreted and present transiently in extracellular matrix but is rapidly internalized for degradation by fibroblasts and endothelial cells. TSP1 is abundant in megakaryocytes and platelets and is constitutively expressed at the dermal-epidermal boundary in skin and in subendothelial matrix of some blood vessels.

### Function

TSP1 binds to extracellular matrix ligands including fibrinogen, fibronectin, some collagens, latent and active transforming growth factor-beta-1, TSG6, heparin, plasmin, cathepsin G, neutrophil elastase, some MMPs, tissue factor pathway inhibitor, and heparan sulfate proteoglycans. TSP1 binds to cell surface receptors including CD36, CD47, some syndecans, LDL receptor-related protein-1 (via calreticulin) and the integrins alpha-V/beta-3, alpha-3/beta-1, alpha-4/beta-1, and alpha-6/beta-1. TSP1 is a slow tight inhibitor of plasmin, cathepsin G, and neutrophil elastase. TSP1 directly binds and activates latent TGF-beta-1. TSP1 in a context-dependent and cell-specific manner stimulates or inhibits cell

adhesion, proliferation, motility, and survival. TSP1 is a potent inhibitor of angiogenesis, but N-terminal proteolytic and recombinant parts of TSP1 have clear pro-angiogenic activities mediated by beta-1 integrins. In the immune system, TSP1 is a potent inhibitor of T cell and dendritic cell activation and mediates clearance of apoptotic cells by phagocytes. In the CNS, TSP1 secreted by astrocytes promotes synaptogenesis.

Based on studies of TSP1 null mice, platelet TSP1 is not essential for platelet aggregation, but TSP1 null mice have impaired wound repair, increased retinal angiogenesis, and are hyper-responsive to several inflammatory stimuli.

### Homology

TSP1 is a member of the thrombospondin family that also contains thrombospondin-2, -3, -4, and cartilage oligomeric matrix protein (COMP). The central type 1 repeats are also known as thrombospondin-repeats and are shared with the larger thrombospondin/properdin repeat superfamily.

## Mutations

### Germinal

a2210g (Asn700Ser) premature familial myocardial infarction; alters Ca-binding to TSP1.

g1678a (Thr523Ser) genetic risk factor of cerebral thrombosis in a Chinese population.

## Implicated in

### Various cancers

#### Disease

Associated with local invasive behavior, tumor neovascularization, and metastasis.

#### Prognosis

Decreased TSP1 expression has been correlated with malignant progression and decreased survival in several cancers. To date, the strongest data is for colorectal carcinomas. Five independent studies involving more than 400 patients have shown significant association of reduced TSP1 expression with increased invasion, microvascular densities, and poor prognosis. More limited studies have shown associations of decreased TSP1 with poor prognosis in squamous non-small cell lung carcinoma, pancreatic adenocarcinoma, invasive cervical carcinoma, and oral squamous cell carcinomas. TSP1 is generally not a useful prognostic factor in breast or prostate cancers, although one study of 58 breast DCIS showed loss of stromal TSP1 in DCIS with more aggressive histological features. Recent evidence indicates that the failure of TSP1 to protect in most breast cancers is due to an escape mechanism involving increased VEGF expression. Finally, TSP1 was positively correlated with invasion in hepatocellular and ovarian carcinomas.

### Oncogenesis

Mutation of THBS1 has not been reported in cancers, but loss of THBS1 expression due to hypermethylation, transcriptional regulation by oncogenes or tumor suppressor genes, or altered mRNA stability has been reported in many cancers. Transgenic mouse models support the tumor suppressor activity of THBS1. Mice lacking TSP1 develop tumors earlier in a p53 null background. Conversely, transgenic mice overexpressing TSP1 in skin or mammary tissue are resistant to chemical or oncogene-driven carcinogenesis.

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