

Gene Section Review

THBS2 (thrombospondin-2)

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Identity

Hugo: THBS2

Other names: TSP2,; CISP (corticotropin-induced secreted protein)

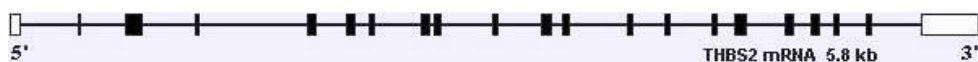
Location: 6q27

Local order: Telomeric to SMOC2 (SPARC related modular calcium binding 2), centromeric to LOC4422783.

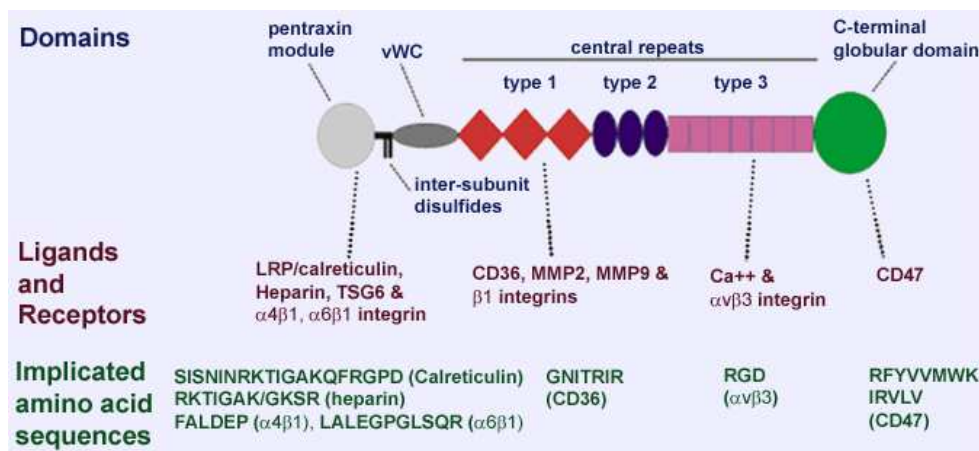
DNA/RNA

Description

The THBS2 gene is 38,261 bases in size and is composed of 23 exons. Exons 3-22 encode the 5,808 base mRNA.



Intron-exon organization of the THBS2 gene.



Domain organization and localization of selected ligand binding sites in TSP2. TSP2 is a homotrimer linked via disulfide bonds. In most cases, sequences recognized by TSP2 receptors are inferred from mutagenesis of the corresponding sequences in TSP1 and supported by peptide inhibition studies using the TSP2 sequences.

The oncogene *c-myc* affects TSP 2 expression via a post-transcriptional regulation of its mRNA stability. Potential transcription factor binding sites have been described for: NF- κ B, NF-Y, p53, Myc-CF1, Sp1, CF-1, GATA and AP-1.

Pseudogene

None described.

Protein

Description

The TSP2 precursor contains 1172 amino acids; 129,955 Da. The mature secreted protein comprises residues 19-1172 and assembles into a disulfide linked homotrimer. Secreted TSP2 is a glycoprotein with a molecular mass of 150-160 kDa that contains approximately 7 potential Asn-linked oligosaccharide attachment sites and variable numbers of C-mannosylated Trp residues in the type 1 repeats. An X-ray crystal structure for the C-terminal regions of TSP2 revealed that the type 3 repeats when replete with Ca wrap around the globular G domain.

Expression

TSP2 is expressed in many tissues during embryonic development, in the healthy adult and in various tumor stromal environments. Predominant expression is found in the connective tissue compartment and based on EST profiling, expression is highest in bone. Mice lacking thrombospondin 2 show an atypical pattern of endocortical and periosteal bone formation in response to mechanical loading. Expression is induced during the later stages of wound repair, during tissue remodeling, in rheumatoid synovium, ovarian follicle development, in wound keratocytes, hypertrophied heart, by ACTH, cAMP analogs and adenylate cyclase activators in bovine adrenocortical cells, in aged mice. Downregulation has been observed in fetal Leydig cells of mice overexpressing human chorionic gonadotropin/luteinizing hormone, herpes simplex 1 infected cells, and in Cyclosporin A-induced gingival overgrowths.

TSP2 expression has been reported in some tumors including invasive breast carcinoma, metastatic malignant melanoma, malignant pleural effusions, cervix of pregnant mice, ischemic brain, aggressive ovarian tumor, gastric cancer, renal cell carcinoma, endometrial cancer, colorectal cancer, chemically-induced skin cancer, osteoclastoma, in ACTH-dependent aldosterone producing adenomas, esophageal cancer. Down regulation of TSP2 was reported in ovarian serous papillary carcinoma, salivary gland carcinoma, invasive cervical cancer, and non-small cell lung cancer.

Localisation

TSP2 is secreted but is present only transiently in

extracellular matrix and is rapidly internalized for degradation by fibroblasts after binding to the cell surface. Degradation is similar to TSP1 removal in that it is LRP- and HSPG-dependent and has similar kinetics. Given its pericellular distribution, TSP2, like TSP1, can modulate cell-matrix interactions and cell behavior.

Function

TSP2 binds to extracellular matrix ligands including, transforming growth factor-beta-1, histidine rich glycoprotein, TSG6, heparin, matrix metalloproteinase-2, and heparan sulfate proteoglycans. TSP2 binds to cell surface receptors including CD36, CD47, LDL receptor-related protein-1 (via calreticulin) and the integrins alpha-V/beta-3, alpha-4/beta-1, and alpha-6/beta-1. In contrast to TSP1, TSP2 does not activate latent TGF-beta-1 but similarly to TSP1, TSP2 contains EGF-like modules that bind calcium in a cooperative manner. TSP2 in a context-dependent and cell-specific manner stimulates or inhibits cell adhesion, proliferation, motility, and survival. TSP2 is a potent inhibitor of angiogenesis mediated by the TSP2 receptor CD36. However, its N-terminal region exhibits pro-angiogenic activities mediated by beta-1 integrins. By way of alpha-4/beta-1, TSP2, like TSP1, modulates T cell behavior in-vitro. TSP2 stimulates chemotaxis, MMP gene expression, and activation-dependent adhesion of T cells. In a model of rheumatoid synovium, cell-based TSP2 therapy had an anti-inflammatory role in-vivo and depleted the tissue of infiltrating T cells. In the CNS, TSP2 secreted by astrocytes promotes synaptogenesis.

TSP2 null mice are viable and fertile but display connective tissue abnormalities associated with a defect in collagen fibrillogenesis that manifests as fragile skin, lax tendons and ligaments. Several defects have been reported in responses of TSP2 null mice to specific stresses. Nulls have an enhanced cutaneous inflammatory response, increased endosteal bone density, increased vascular density in dermis, adipose and thymus, a prolonged bleeding time. Fibroblasts isolated from TSP2 nulls are defective in adhesion. In response-to-injury models, TSP2 null mice have an increased vascularity of wounds with a concomitant increase in activity of MMP2 and MMP9 and demonstrate enhanced wound repair.

Homology

TSP2 is a member of the thrombospondin family that also contains thrombospondin-1, thrombospondin-3, thrombospondin-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

t3949g substitution in the 3'-untranslated region is associated with a reduced risk of premature myocardial infarcts.

Somatic

LOH in markers proximal to THBS2 were reported in salivary carcinomas, but disruption of the THBS2 gene has not been confirmed to date.

Implicated in

Various cancers

Disease

Loss of TSP2 expression is associated with local invasive behavior, tumor neovascularization, and metastasis.

Prognosis

Decreased TSP2 expression has been correlated with malignant progression and angiogenesis in some but not all cancers. In a study of 37 gliomas, a lack of TSP2 expression was significantly associated with higher histological grade ($P = 0.0019$) and increased vessel counts and density ($p < 0.0001$). In a study of 61 colon cancers, those expressing TSP2 showed a lower incidence of hepatic metastasis than those not expressing TSP2 ($p = 0.02$). TSP2 negative/VEGF-189 positive colon cancers showed significantly increased vessel counts and density in the stroma ($P < 0.0001$). Finally, in a study of 10 normal cervix and 78 invasive cervical cancer samples, TSP2 mRNA expression in normal cervix was significantly higher than that in cervical cancer ($p = 0.032$). Microvessel counts were marginally increased in the cervical cancer patients lacking TSP2 mRNA expression ($p = 0.062$). To date, the numbers of specimens examined for each of these cancers are too small to evaluate the independent prognostic value of TSP2 expression.

Conversely, TSP2 was strongly expressed in a series of melanoma metastases, but not in primary tumors, and in 55 endometrial cancer specimens TSP2 expression was significantly higher in malignancies exhibiting cervical and lymph-vascular space involvement ($p = 0.029$ and $p = 0.009$, respectively).

Oncogenesis

Somatic mutation of THBS2 has not been clearly established in human cancers, but loss of TSP2 expression due to hypermethylation of its promoter was reported in a study of endometrial carcinomas. LOH in 6q15-27 between D6S297 and D6S1590 was reported in a study of salivary gland carcinomas and associated in 8 of 9 cases with loss of TSP2 expression.

Transgenic mouse models support the tumor suppressor activity of THBS2. Tumor progression of chemically-

induced skin cancer is accelerated in TSP2 null mice, and there is an increased rate of lymph node metastases. The correlated increase in vessel density and size in these nulls also supports a suppressive role for TSP2. Tumor growth and angiogenesis are delayed and decreased when TSP2 is overexpressed in this model. Mouse models have also been used to explore therapeutic use of TSP2 to limit tumor growth and angiogenesis. These utilize a cell-based approach wherein TSP2 cDNA is transfected into a variety of cells including: glioblastoma, fibrosarcoma, squamous cell carcinoma and breast carcinoma cells. In turn, these TSP2 overexpressing cells when injected subcutaneously into immunodeficient mice exhibit decreased tumor growth and angiogenesis.

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