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Gene Section
Review

ADAMTS1 (ADAM metallopeptidase with thrombospondin type 1 motif, 1)

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Identity

Other names: ADAM-TS1; C3-C5; EC 3.4.24.-; KIAA1346; METH-1; METH1

HGNC (Hugo): ADAMTS1

Location: 21q21.3

Note: Mouse: 16 region C3-C5.

DNA/RNA

Description

Gene : 1 --> 4670.
Exon : 1 --> 1185.
CDS : 456 --> 3359.
Signal peptide : 456 --> 602.
Proprotein: 603 --> 3356.
Mature peptide : 1212 --> 3356.
Human ADAMTS1 DNA spans 4,649 bps. Its sequence is composed of 9 exons.

Transcription

The ADAMTS1 gene is composed of nine exons, all of which are present within the 9.2-kb genomic region. Sequence analysis shows that the open reading frame of ADAMTS1 codes for a protein of 950 amino acids (Vazquez et al., 1999). Among these exons, exons 2 to 8 range from 133 to 347 bp in size. The first and the last exons are longer than the others. There are 4 polyadenylation signals in the untranslated region of exon 9. Exons 1, 5, and 6 encode a proprotein domain, a disintegrin-like domain and a TSP type I motif, respectively, of the ADAMTS1 protein. The metalloproteinase domain is encoded by the 3 exons: 2, 3 and 4. Exons 7 and 8 encode the spacer region (Kuno et al., 1997a).
ADAMTS1 is an IL-1 inducible gene since ADAMTS1 mRNA levels are enhanced 2 h after IL-1 stimulation (Kuno et al., 1997a). Moreover, ADAMTS1 mRNA expression is significantly enhanced in heart and kidney after lipopolysaccharide (LPS) treatment. These data indicate that the ADAMTS1 gene is an inflammation-associated gene.

Pseudogene

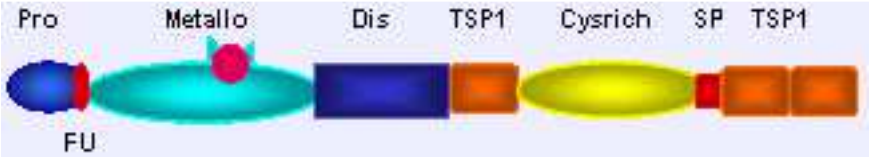
No pseudogenes reported.

Protein

Note
ADAMTS1 precursor: 967 amino acids; 105358 Da.

Description

There are many cysteine residues, especially from residues 346 to 950, and four putative N-glycosylation sites in the ADAMTS1 protein. Comparison of the deduced amino acid sequence of ADAMTS1 protein with the data base (Human Genome Center, Institute of Medical Science, University of Tokyo) reveales that the middle part (519-615 amino acids) of the ADAMTS1 gene product shows about 40% homology with thrombospondin-1 and thrombospondin-2 (Kuno et al., 1997b).
The TSP type I motifs present in the C-terminal half of ADAMTS1 are functional for binding to heparin. Moreover, analyses of deletion mutants have revealed that the carboxyl-terminal spacing region as well as three TSP type I motifs are responsible for the anchoring to the extracellular



Structure of ADAMTS1 proteinase. ADAMTS1 is composed of a propeptide (Pro), a metalloproteinase domain (Metallo), a disintegrin domain (Dis), a thrombospondin type 1-like motif (TSP1), a cystein-rich domain (Cysrich), a spacer domain (SP) followed by two additional thrombospondin type 1-like motifs (TSP1). ADAMTS1 proteinase contains in addition a sequence recognized by furin-like enzymes (FU) (Rocks et al., 2008a).

matrix (Kuno and Matsushima, 1998).
The proteinase domain of ADAMTS1 is capable of forming a covalent complex with alpha2-macroglobulin, a plasma proteolytic enzyme inhibitor that binds various types of proteinases, revealing that ADAMTS1 is an active metalloproteinase. The finding that a mutation of the zinc-binding motif of ADAMTS1 abrogates its capacity to bind to alpha2-macroglobulin confirmes the notion of an active proteinase (Kuno et al., 1999). However, in the potential zinc-binding motif of ADAMTS1, the Gly residue of the consensus sequence (HEXXHXXGXXH) is not conserved. Since ADAMTS1 is an active metalloproteinase, it is likely that the conserved Gly residue of the zinc-binding motif is functionally interchangeable with Asn (Kuno et al., 1999).
Studies have demonstrated that ADAMTS1 and fibulin-1 are colocalized in vivo. Interestingly, fibulin-1 has been found to enhance the capacity of ADAMTS1 to cleave aggrecan. Fibulin-1 seems therefore to be a new regulator of ADAMTS1-mediated proteoglycan proteolysis and may play an important role in proteoglycan turnover in tissues where there is overlapping expression (Lee et al., 2005).

Expression

To date, studies analyzing the expression of ADAMTS1 in normal tissues have leaded to controversial data. Tissue distribution of ADAMTS1 mRNA has been examined by Northern blot analysis by several research groups. While some research groups describe a very weak signal for ADAMTS1 mRNA in the heart and kidney and no ADAMTS1 mRNA expression in other organs including lung, liver, brain, and muscle, other groups describe an ADAMTS1 expression in every tissues analyzed, with abundant ADAMTS1 mRNA expression in adrenal, heart, and placenta, skeletal muscle, thyroid, and stomach. Of the embryonic tissues analyzed, kidney has showed the highest expression of ADAMTS1 mRNA. ADAMTS1 mRNA has been detected in dermal fibroblasts and at lower levels in vascular smooth muscle cells, endometrial stromal cells and in some endothelial cells (Vazquez et al., 1999).
Since the ADAMTS1 gene is activated by IL-1 stimulation in vitro, LPS has been administered intravenously into mice for induction of systemic inflammation. ADAMTS1 mRNA levels are significantly enhanced in heart and kidney after LPS treatment, but not in other organs (evaluated by Northern blot analysis). This result indicates that the ADAMTS1 gene is an inflammation-associated gene (Kuno et al., 1997b).
ADAMTS1 mRNA has been detected in the ischemic myocardium. Endothelial cells, which weakly express ADAMTS1 mRNA in the normal heart, have shown increased expression of ADAMTS1 mRNA immediately after myocardial infarction concomitant with VEGF expression (Nakamura et al., 2004).
Increased ADAMTS1 mRNA expression has been observed in the kidney by in situ hybridization after induction of unilateral ureteral obstruction (Nakamura et al., 2007).
In granulosa cells, progesterone receptor appears to play the role of an inducible coregulator of the ADAMTS1 gene (Doyle et al., 2004).

Localisation

Extracellular localization, anchored to the extracellular matrix through C-terminal spacing region and thrombospondin type I motifs.

Function

ADAMTS1 is a catalytic active protein and identified substrates of ADAMTS1 are principally proteoglycans such as aggrecan and versican (Kuno et al., 2000; Rodriguez-Manzaneque et al., 2002).
ADAMTS1 is able to cleave ligands of the EGF (Epidermal Growth Factor) receptor such as pro-HBEGF (Heparin-binding EGF-like Growth Factor) or pro-amphiregulin (Liu et al., 2006).
Two new substrates of ADAMTS1 have been identified recently: thrombospondin-1 and thrombospondin-2 (Lee et al., 2006).
Like many members of the ADAM and ADAMTS subfamilies, ADAMTS1 shares many physiological and pathological functions. Studies using ADAMTS1-knock-out mice showed that this proteinase is important for normal growth, organogenesis and fertility (Mittaz et al., 2004).
ADAMTS1 is implicated in inflammatory processes since a treatment of mice with LPS enhances ADAMTS1 expression in tissues (Kuno et al., 1997b).

Homology

Comparison of the human and mouse sequences of ADAMTS1 reveals highly conservation (83.4% amino

acid identity). The overall amino acid sequence identity between ADAMTS1 and ADAMTS-8 is 51.7% (Vazquez et al., 1999).

Mutations

Note

A down-regulation of ADAMTS1 has been observed in some non small cell lung cancer (NSCLC) cell lines and is concordant with an aberrant methylation of the gene. In NSCLC tumours, aberrant methylation of the gene has been observed in 31.6% of samples, while it was found in only 7.1% of nonmalignant tissues (Choi et al., 2008).

In colorectal tumors, ADAMTS1 gene is associated to a cancer-specific hypermethylation. Among 20 colon cancer cell lines, hypermethylation of the ADAMTS1 gene was identified in 85% of cell lines. The methylation status of ADAMTS1 has also been investigated in colorectal adenomas and carcinomas. 37% of adenomas as well as 71% of carcinomas showed hypermethylation for the ADAMTS1 gene. However, ADAMTS1 is unmethylated in tumors from three other organs, prostate, testis, and kidney (Lind et al., 2006).

Implicated in

Lung cancer

Note

ADAMTS1 stable transfection in human epithelial lung cancer cells (BZR) accelerates the in vivo tumor growth after subcutaneous injection of cell transfectants into severe combined immunodeficient (SCID) mice (Rocks et al., 2008a).

The proteolytic status of ADAMTS1 is determinant for its effects on tumor metastasis since the catalytically inactive ADAMTS1 and the ADAMTS1 fragments generated by auto-proteolytic cleavage inhibit tumor metastasis of cells subcutaneously injected into mice by negatively regulating the availability and activity of soluble heparin-binding EGF (HB-EGF) and amphiregulin (Liu et al., 2006).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

Tumours derived from ADAMTS1 overexpressing cells display an enhanced stromal reaction characterized by a myofibroblast infiltration and excessive matrix deposition (Rocks et al., 2008b). These features are, however, not observed in tumors derived from cells overexpressing a catalytically inactive mutant of ADAMTS1. A Boyden Chamber assay has shown that conditioned media from ADAMTS1-overexpressing cells display a potent chemotactic activity towards fibroblasts. Moreover, ADAMTS1 overexpression in tumors is associated with increased production of matrix metalloproteinase-13, fibronectin, transforming growth factor (TGF) beta, and interleukin (IL)-1 beta. Neutralizing antibodies against TGF-beta and IL-1 beta block the chemotactic effect of medium conditioned by ADAMTS1-overexpressing cells on fibroblasts, showing the contribution of these factors in ADAMTS1-induced stromal reaction (Rocks et al., 2008b).

Moreover, overexpression of ADAMTS1 in Lewis lung carcinoma cells promotes pulmonary metastasis of these cells. Interestingly, the proteinase-dead mutant of ADAMTS1 inhibits their metastasis, indicating again that the prometastatic activity of ADAMTS1 requires its metalloproteinase activity. Overexpression of ADAMTS1 in these cells promotes tumor angiogenesis and invasion, shedding of the transmembrane precursors of HB-EGF and amphiregulin. This study shows that ADAMTS1 undergoes auto-proteolytic cleavage to generate the NH2- and COOH-terminal cleavage fragments containing at least one thrombospondin-type-I-like motif. Overexpression of the NH2-terminal ADAMTS1 fragment and the COOH-terminal ADAMTS1 fragment inhibits pulmonary tumor metastasis (Liu et al., 2006).

Breast cancer

Note

Real-Time PCR analysis of human breast tissues shows that ADAMTS1 is downregulated in breast carcinomas in respect to non neoplastic mammary tissue, irrespective of the heterogeneity of the samples and the tumor type or grade. ADAMTS1 is expressed predominantly in stromal fibroblasts (Porter et al., 2004).

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Pancreatic cancer

Note

ADAMTS1 expression has been identified in pancreatic cancer cell lines and quantified by TaqMan reverse transcription-PCR in 18 paired samples of pancreatic cancer and surrounding noncancerous pancreas. ADAMTS1 expression in pancreatic cancer tissue is significantly lower than that in noncancerous pancreas (Masui et al., 2001).

Prognosis

Pancreatic cancer displaying higher ADAMTS1

expression show significantly severe lymph node metastasis or retroperitoneal invasion and worse prognosis. ADAMTS1 seems to be involved in progression of pancreatic cancer through local invasion and lymph node metastasis (Masui et al., 2001).

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Myocardial infarction

Note
Normal endothelium expresses little ADAMTS1 mRNA, and normal myocardium expresses no detectable ADAMTS1 mRNA. In situ hybridization has revealed strong ADAMTS1 mRNA signals in the endothelium and myocardium in the infarcted heart, mainly in the infarct zone. The rapid and transient up-regulation of the ADAMTS1 gene in the ischemic heart is distinct from the regulatory patterns of other MMPs (Nakamura et al., 2004).

Prognosis
Not determined.

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Normal growth, organogenesis, fertility

Note
ADAMTS1 is produced by the granulosa cells of ovarian follicles. Mice with ADAMTS1 gene disruption are subfertile due to a significant reduction in the number of healthy growing follicles. Follicle dysmorphogenesis starting at the stage of antrum formation was identified in ADAMTS1 -/- ovaries. ADAMTS1 is therefore necessary for structural remodelling during ovarian follicle growth (Brown et al., 2006). In addition, ovulation in ADAMTS1 null females was impaired because of mature oocytes remaining trapped in ovarian follicles. Moreover, forty-five percent of newborn ADAMTS1 null mice die, with death most likely caused by a kidney malformation that becomes apparent at birth (Mittaz et al., 2004). These mice present enlarged renal calices with fibrotic changes from the ureteropelvic junction through the ureter, and abnormal adrenal medullary architecture without capillary formation (Shindo et al., 2000).

Prognosis
Not determined.

Cytogenetics
Not determined

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Angiogenesis inhibitor

Note
ADAMTS1 suppresses fibroblast growth factor-2 (FGF2)-induced vascularization in the cornea pocket assay and inhibits VEGF-induced angiogenesis in the chorioallantoic membrane assay. ADAMTS1 binds to VEGF and therewith abrogates the phosphorylation of its receptor, VEGFR2 (Vazquez et al., 1999).

Prognosis
Not determined.

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Renal ischemia or obstruction

Note
Rats subjected to bilateral renal ischemia display an enhanced expression of ADAMTS1 in renal tissues. Immunofluorescence localized the ADAMTS1 expression to proximal tubules following ischemia-reperfusion injury. An inhibition of the VEGF pathway by ADAMTS1 during the early injury and repair phase of renal ischemia may therefore contribute to an overall reduction in renal microvascular density (Basile et al., 2008).
Increased ADAMTS1 mRNA expression (in situ hybridization) has also been observed in the kidney of rats after induction of unilateral ureteral obstruction. The mRNA is then localized in the renal tubular epithelial cells in the outer stripe of the outer medulla (Nakamura et al., 2007).

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Oncogenesis
Not determined.

Asthma

Note
Expression profile of several ADAM and ADAMTS proteinases has been measured in sputum cells from patients with asthma. The relationship between the expression of these proteinases and asthma-associated inflammation and airway obstruction has been assessed. Levels of ADAMTS1 mRNA are

significantly decreased in patients with asthma compared to control patients (Paulissen et al., 2006).

Prognosis
ADAMTS1 expression is positively correlated to Forced Expiratory Volume at the first second (FEV(1)) ($r = 0.45$, $P < 0.05$) (Paulissen et al., 2006).

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

New bone formation

Note
ADAMTS1 mRNA expression has been identified by RT-PCR in cultures of rat osteoblasts treated with molecules known to drive osteoblast differentiation (ascorbic acid, beta-glycerophosphate and dexamethasone). ADAMTS1 expression follows the expression of osteogenic marker osteocalcin during in vitro mineralization. ADAMTS1 production has been investigated by immunostaining during in vitro osteogenesis and in sections from 2- and 10-day-old rat femur. These results show a strong expression of ADAMTS1 around mineralized nodules and intense focal staining of putative new areas of nodule formation in vitro. In 2- and 10-days-old rat femurs, ADAMTS1 protein is localized in regions associated with osteogenesis. These data show that ADAMTS1 protein accumulates in osteoblast extracellular matrix during differentiation (Lind et al., 2005).

Prognosis
Not determined.

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

Neurodegenerative disorders

Note
Levels of ADAMTS1 have been assessed in extracted proteins from Down syndrome (DS) brain and brains of patients with Alzheimer's (AD) and Pick's disease (PD) used as controls. ADAMTS1 immunoreactivity is increased in brains with DS and neurodegeneration. Overexpression of this metalloproteinase might thus be involved in proteoglycan degradation and handling in brain of patients with neurodegenerative disease which in turn may lead to or reflect pathological lesions in DS, AD and PD brain (Miguel et al., 2005).

Prognosis
This overexpression of ADAMTS1 may be used as marker protein for neurodegeneration.

Cytogenetics
Not determined.

Hybrid/Mutated gene
Not determined.

Abnormal protein
Not determined.

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