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Review

ADAMTS12 (ADAM Metallopeptidase With Thrombospondin Type 1 Motif, 12)

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Abstract

Review on ADAMTS12, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: PRO4389

HGNC (Hugo): ADAMTS12

Location: 5p13.3

DNA/RNA

Description

24 exons, spans approximately 368.66 Kb of genomic DNA in the telomere-to-centromere orientation.
The translation initiation codon is located to exon 1, and the stop codon to exon 24.

Transcription

ADAMTS12 Human mRNA of 8.77 Kb as detected by northern-blot.

Protein

Description

The open reading frame encodes a 1594 amino acid protein, with an estimated molecular weight of 178 kDa. ADAMTS-12 shares a structural multidomain complex architecture with the rest of members of the ADAMTS family. This organization includes a signal peptide, a prodomain involved in maintaining enzyme latency and a catalytic domain that contains the consensus sequence HEXXHGXXHD involved in the coordination of the zinc atom necessary for catalytic activity of the enzyme. This sequence ends in an Asp residue which distinguishes ADAMTSs from other metalloproteases such as MMPs. Following this catalytic region there are several other domains characterized as a disintegrin-like domain, a central thrombospondin-1 (TSP-1) motif, a cysteine-rich domain, a spacer region and a variable number of TSP-1 repeats, three in the case of ADAMTS-12. A structural hallmark of ADAMTS-12 is the presence of a second spacer region followed by four additional TSP-1 repeats (Figure 1) (Cal et al., 2001).

Expression

ADAMTS12 cDNA was originally cloned from a human fetal lung cDNA library and its expression was also detected in human fetal fibroblasts following treatment with TGF-β. By real-time polymerase chain reaction (PCR) assay ADAMTS12 expression can also be detected in cartilage, synovium, tendon, skeletal muscle and fat. ADAMTS12 was also found widely expressed in gastrointestinal, pancreatic and colon carcinomas but not in the paired normal tissues, suggesting that this enzyme could also participate in the development and/or progression of tumors from different origin (Cal et al., 2001; Liu et al., 2006; Moncada-Pazos et al., 2009).

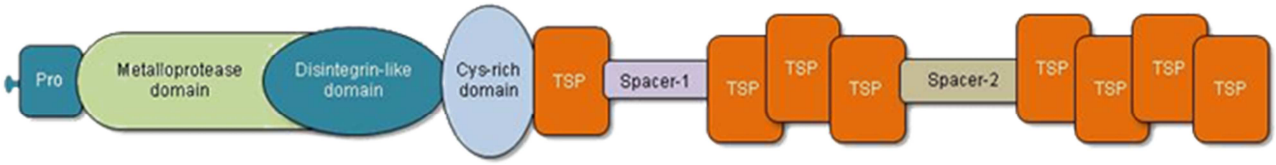

Figure 1. Domain organization of ADAMTS-12. Pro: prodomain; TSP: thrombospondin type-1 domains.

Localisation

Extracellular.

Function

Several studies performed to characterized ADAMTS-12 function indicate its role as being a host-protective enzyme with antitumor properties (Llamazares et al., 2007; Moncada-Pazos et al., 2009; El-Hour et al., 2010; Wang et al., 2011). Additionally, ADAMTS-12 has a role in trophoblasts invasion during placental development which is independent of the proteolytic domain (Beristain et al., 2011).

ADAMTS-12 also participates in other pathological processes such as inflammation, allergen-induced inflammation and hyperresponsiveness, and it is also involved in arthritic processes (Liu, 2009; Moncada-Pazos et al., 2012; Nah et al., 2012; Paulissen et al., 2012).

Furthermore, different genomic approximations have described how other human pathologies like asthma, schizophrenia or predisposition to pediatric stroke are related to ADAMTS12 locus (Kurz et al., 2006; Arnin et al., 2012; Bespalova et al., 2012). However, besides its participation in pathological situations little is known about ADAMTS-12 partners and/or substrates in normal or pathogenic processes.

Homology

The ADAMTS12 gene is conserved in chimpanzee (Refseq: XP_517836), macaque (Refseq: XM_001090049), dog (Refseq: XM_536508), cow (Refseq: NM_001192609), mouse (Refseq: NM_175501), rat (Refseq: NM_001106420), chicken (Refseq: XM_003642975), and zebrafish (Refseq: XM_001343335).

ADAMTS-12 belongs to the A Disintegrin And Metalloprotease Domains with ThromboSpondin motifs (ADAMTS) family, which consists of 19 secreted zinc metalloproteinases (Porter et al., 2005).

All members of the family share the same structural domain design.

ADAMTS-12 is closely related to ADAMTS-7 since both proteins display the C-terminal TSP residues separated by two spacer regions (spacer-1 and spacer-2).

The rest of the members contain only one spacer region followed by a variable number of TSP domains.

Implicated in

Various cancers

Note

Different studies have highlighted the role of ADAMTS12 as a tumor-suppressor gene. ADAMTS-12 is able to alter the tumorigenic effects of hepatocyte growth factor (HGF) in Madin-Darby canine kidney (MDCK) cells (Llamazares et al., 2007). ADAMTS-12 also prevents the formation of tubules by bovine aortic endothelial cells in the presence of vascular endothelial growth factor (VEGF). Additionally, growth of subcutaneous tumors induced by the human lung tumor cell line A549 is compromised when ADAMTS12 is exogenously expressed. Analysis of the epigenetic status of ADAMTS12 promoter has reinforced the role of ADAMTS-12 as an in vivo tumor-suppressor enzyme. In fact, ADAMTS12 is epigenetically silenced in tumor cells from different sources such as colon cancer cell lines, breast cancer cell lines, cervix cancer cell lines or lymphoma cell lines (Moncada-Pazos et al., 2009). In particular, methylation levels of ADAMTS12 gene promoter were very high in a colon cancer sample panel that included both cancer cell lines and tumor samples, whereas it was found not or barely methylated in normal cells and tissues. However and similar to what has been found in gastrointestinal and pancreatic carcinomas, ADAMTS12 expression was higher in colon tumor samples cells than in normal tissues. This apparent contradiction resides in the fact that ADAMTS-12 is produced by the stromal cells surrounding neoplastic cells and not by the tumor cells themselves, which was confirmed using different approaches. For instance, immunofluorescence techniques allowed the localization of this protease in the proximity to alpha smooth muscle actin positive cells, which suggests that cancer-associated fibroblasts could be responsible for ADAMTS12 expression. By contrast, ADAMTS-12 staining resulted negative in the case of tumor cells. ADAMTS12 expression in fibroblasts was verified through the use of co-cultures of colon fibroblasts with colon cancer cells. Furthermore, this expression could be associated with a functional effect as colon cancer cells showed minor growth rates and an increase in apoptosis when co-cultured with colon fibroblasts in comparison to the colon tumor cell line cultured alone. Consequently,

colon miofibroblast-ADAMTS12 expression could be part of a protective response aimed to compensate for the epigenetic silencing of this gene in tumor cells (Moncada-Pazos et al., 2009). Moreover, ADAMTS12 expression in colorectal cancer significantly correlated with the tumor histological grade, depth of tumor invasion, lymph node metastasis, and Duke's stage. In fact, patients with low or no ADAMTS12 expression in the tumor stroma had a significantly poor overall survival or disease-free survival (Wang et al., 2011). Phenotypic analysis of the Adamts12-deficient mouse has confirmed the role of this metalloprotease as a tumor-protective enzyme (El-Hour et al., 2010).

This mouse develops normally and does not show any obvious phenotype. However, different models to analyze the angiogenesis process in vivo, including malignant keratinocyte transplantation, aortic ring assay and Matrigel plug, supported that this protease exhibits anti-angiogenic properties (El-Hour et al., 2010). Additionally, both intact ADAMTS-12 and a catalytically inactive form of ADAMTS-12 showed a similar ability to inhibit the spreading of endothelial cells. These data were in line with the previous results indicating that antitumor functions of ADAMTS-12 do not depend on its metalloprotease domain (Llamazares et al., 2007).

However, there are some data showing that ADAMTS-12 could also be a potential pro-tumor agent (Beristain et al., 2011). Thus, in placental cytotrophoblasts the expression of ADAMTS12 is able to exploit the same molecular machinery found in metastatic carcinoma cells. Comparing ADAMTS-family members-expression in highly versus poorly invasive cells during placental development, ADAMTS12 was preferentially expressed by the highly invasive cytotrophoblast cell line EVT.

Furthermore, TGF-β or IL-1β, are also able to respectively induce or restrain ADAMTS12 expression in these cells as they also did in colon fibroblasts. Analyzing the domains involved in this process demonstrated how the metalloprotease domain does not fulfill a relevant role in this pro-invasive phenotype (Beristain et al., 2011).

In summary, there are several studies suggesting ADAMTS-12 as being involved in tumor progression.

Nowadays, more data indicate this protein as a new member of the growing type of metalloproteases showing tumor-suppressor properties (Lopez-Otin and Matrisian, 2007). However, some data indicate a different role for this gene specifically regarding cellular invasion, which suggest that ADAMTS-12-function in tumor progression might depend on different interactions occurring within the extracellular microenvironment.

Inflammation

Note

Loss-of-function of Adamts-12 enhances mouse susceptibility to inflammatory processes (Moncada-Pazos et al., 2012). In this sense, it has been shown how Adamts12 deficiency is responsible for increase inflammation in mice that was not limited to a certain tissue as it was a common phenomenon affecting several organs. Different experimental conditions to induce colitis, endotoxic sepsis, pancreatitis or allergen-induced lung inflammation demonstrated that absence of ADAMTS-12 resulted in a more severe inflammation phenotype as well as a delayed recovery from these anomalies. These changes were accompanied by an increase in inflammatory markers and, at the same time, the clinical symptoms observed in Adamts12-deficient mice were also concomitant with neutrophilia or eosinophilia and mast cells recruitment in affected tissues (Moncada-Pazos et al., 2012; Paulissen et al., 2012). In vitro culture of human neutrophils indicated that the presence of ADAMTS-12 might be a player in inducing neutrophil clearance, a required step for the resolution of an inflammation process.

Arthritis

Note

ADAMTS-12 shows aggrecan-degrading activity, similarly to aggrecanases ADAMTS-4 and ADAMTS-5, and to other members of the family such as ADAMTS-1, ADAMTS-9, ADAMTS-15, ADAMTS-16 and ADAMTS-18 (Lin and Liu, 2010). Nevertheless, the ability of ADAMTS-12 to degrade aggrecan is reduced and it has only been reported to occur in vitro (Llamazares et al., 2007). Although barely detectable in adult tissues real-time polymerase chain reaction (PCR) assay revealed ADAMTS12 expression in cartilage, synovium, tendon, skeletal muscle and fat (Liu et al., 2006). In vitro experiments have also been used to demonstrate ADAMTS-12 proteolytic activity towards cartilage oligomeric matrix protein (COMP), other component of cartilage. This, together with ADAMTS-12 aggrecanolytic activity, may indicate a role of ADAMTS-12 in arthritic diseases (Liu et al., 2006). In this regard, profiling analysis demonstrated a significant upregulation of ADAMTS-12 in cartilage from patients with osteoarthritis when compared with normal cartilage (Kevorkian et al., 2004). Thus, ADAMTS-7 and ADAMTS-12, apart from the known aggrecanases ADAMTS-4 and -5, seem to be important players in the degradation of components of cartilaginous tissue during arthritic processes (Liu, 2009). In relation to potential endogenous inhibitors, it has been described that α2-macroglobulin and the granulin-epithelin precursor, a growth factor highly expressed in chondrocytes, can interact with

ADAMTS-12, leading to an inhibition of its COMP-degrading activity (Luan et al., 2008; Guo et al., 2010).

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