Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

ADAMTS15 (ADAM Metallopeptidase With Thrombospondin Type 1 Motif, 15)

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Published in Atlas Database: February 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/ADAMTS15ID45587ch11q24.html
DOI: 10.4267/2042/54032

Abstract

Review on ADAMTS15, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

HGNC (Hugo): ADAMTS15

Location: 11q24.3

DNA/RNA

Description

8 exons, spans approximately 27.66 Kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon is located to exon 1, and the stop codon to exon 8.

Protein

Description

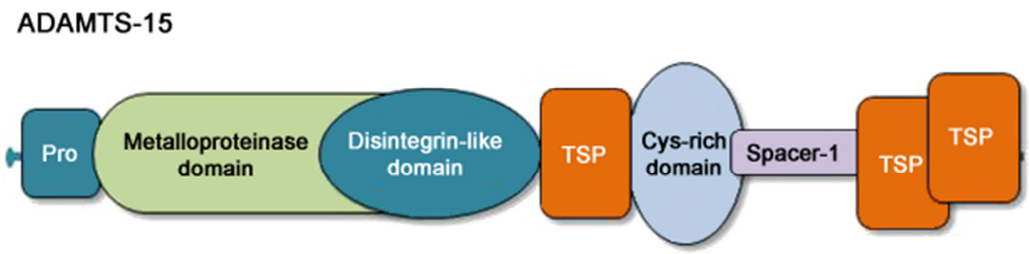
The open reading fame encodes a 950 amino acid protein, with an estimated molecular weight of 103,2 kDa. ADAMTS-15 shares a structural multidomain complex architecture with the rest of the members of the ADAMTS family.

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 activiy 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 disintegrin-like domain, a central thrombospondin-1 (TSP-1) motif, a cysteine-rich domain, a spacer region and two more TSP-1 domains (Cal et al., 2002).

Expression

ADAMTS15 cDNA was originally cloned from both, a human liver and kidney fetal cDNA library (Cal et al., 2002).



Domain organization of ADAMTS-15. Pro: prodomain; TSP: thrombospondin type-1 domains.

Later on, in the search for proteinases and proteinase inhibitors in articular cartilage from femoral heads of patients with end-stage osteoarthritis (OA) Kevorkian et al. found high levels of ADAMTS-15 expression in samples from both, OA patients as well as normal controls (Kevorkian et al., 2004). In relation with ADAMTS-15 participation in tumor progression its expression has been described in either normal cells or cells adjacent or marginal to cancer tissue in samples from colon adenocarcinoma as well as in samples from head and neck squamous cell carcinoma (Viloria et al., 2009; Stokes et al., 2010). Additionally ADAMTS-15 presence has also been detected in some breast and prostate cancer cell lines (Molokwu et al., 2010).

Localisation

Extracellular, mostly pericellular.

Function

Few studies describe ADAMTS-15 function beyond those describing its participation in cancer and osteoartritic processes. Regarding cancer, ADAMTS-15 has recently emerged as a putative tumor suppresor gene since it is downregulated in breast cancer, and functionally inactivated through specific mutations in colorectal cancer (Porter et al., 2004; Porter et al., 2006; Viloria et al., 2009). In addition, aberrant expression of ADAMTS-15 is implicated in prostate cancer progression (Molokwu et al., 2010). The latest apparently results from the relationship between ADAMTS-15 expression and versican degradation. Thus, ADAMTS-15 seems to be acting as a versican-degrading enzyme whose accumulation potentially contributes to prostate cancer pathology (Cross et al., 2005). In this regard, versican seems to be one of the targets of ADAMTS-15 proteolityc activity which involves this protein in processes such as cancer or skeletal muscle fiber formation (Croos et al., 2005; Stupka et al., 2013; Dancevic et al., 2013).

Homology

ADAMTS-15 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-15 is, among all the members, closely related to ADAMTS-1 which suggested its involvement in angiogenic processes (Cal et al., 2002).

The ADAMTS15 gene is conserved in chimpanzee (Refseq: XM_522253), macaque (Refseq: XM_001113698), dog (Refseq: XM_005620295), cow (Refseq: NM_001192390), mouse (Refseq: NM_001024139), rat (Refseq: NM_001106810), chicken (Refseq: XM_417874), and zebrafish (Refseq: XM_001341842).

Mutations

Somatic

ADAMTS15 was identified as one of the so-called CAN genes found to be mutated in a small set of colorectal cancers (Sjöblom et al., 2006). Two heterozigous somatic mutations were described out of eleven human cancer samples (cDNA: 2309A>G, cDNA: 2632T>G). Functional relevance of mutations found in colorectal cancer were described for a deleterious single base mutation 24544ΔG affecting the two carboxy-terminal thrombospondin motifs of ADAMTS-15 (Viloria et al., 2009). The derived truncated form of ADAMTS-15 (ADAMTS15_G849fs) is barely found in the pericellular space of the cell being mostly liberated to the culture media. Functional studies revealed ADAMTS15_G849fs not showing the anti-tumoral properties of full length ADAMTS-15. In the same study, three other mutations where identified, a base pair mutation affecting the second TSP-1 domain (24616C>T), a silent base pair change (13777C>T) and another base deletion generating a completely truncated form of ADAMTS-15 (366Δ) (Viloria et al., 2009).

Implicated in

Various cancers

Note

ADAMTS-15 has recently emerged as a putative tumor suppresor gene since it is downregulated in breast cancer, and functionally inactivated through specific mutations in colorectal cancer (Porter et al., 2006; López-Otín et al., 2009; Viloria et al., 2009). In addition, aberrant expression of ADAMTS-15 is implicated in prostate cancer progression (Cross et al., 2005; Molokwu et al., 2010). The first indication regarding a potential protective role for ADAMTS15 derived from the observation that low ADAMTS15 expression levels coupled to high ADAMTS8 levels conferred poor prognosis to breast cancer patients (Porter et al., 2006). Moreover, ADAMTS15 was identified as one of the so-called CAN genes found to be mutated in a small set of colorectal cancers (Sjöblom et al., 2006). Functional support to the putative relevance of ADAMTS-15 as a tumor suppresor protease was described after finding four additional mutations in ADAMTS-15 gene sequence in human colon carcinomas (Viloria et al., 2009). Two of the new mutations resulted in the generation of truncated forms of ADAMTS-15, one of them lacking the last two thrombospondin domains whereas the other originating a complete ADAMTS-15 knock-down.

Functional analysis revealed that the presence of the two last thrombospondin domains is important for the pericellular loacalization of ADAMTS-15 and affects the anti-tumoral function of full length ADAMTS-15 (Viloria et al., 2009; Dancevic et al., 2013).
More recently, ADAMTS-15 has been described as a head and neck squamous cell carcinoma (HNSCC)-associated proteinase since its expression is elevated (together with ADAMTS-1 and ADAMTS-8) in areas surrounding HNSCC tumor microenvironment (Demircan et al., 2009; Stokes et al., 2010).
In addition, these three members of the ADAMTS family have elevated expression levels in HNSCC tumor versus normal tissue and in HNSCC derived cell lines vs normal keratinocytes (Stokes et al., 2010).
ADAMTS-15 has also been indirectly involved in androgen-mediated prostate cancer growth and proliferation, function that depends on ADAMTS-15 versicanolytic activity (Cross et al., 2005; Molokwu et al., 2010).
Molokwu et al identified one androgen-responsive element (ARE) in ADAMTS-15 promoter and 12 more AREs in its gene sequence. In the same article the authors demonstrated ADAMTS-15 reduction both, at mRNA and protein levels, in the presence of dihidrotestorone (DHT).
ADAMTS-15 down-regulation in prostate cancer resulted in high versican levels which is a poor prognosis indicator in these type of tumors (Ricciardelli et al., 1998; Luo et al., 2002; Molokwu et al., 2010).

Colon cancer

Note

ADAMTS15 expression inversely correlates with histopathologic differentiation grade in human colorectal carcinomas when analyzing ADAMTS-15 inmunostaining in normal colon epithelia, well-differentiated tumors, moderately differentiated tumors, and poorly differentiated colorectal carcinomas (Viloria et al., 2009).

Head and neck squamous carcinoma (HNSCC)

Note

ADAMTS15 mRNA levels, together with those of other ADAMTS members (ADAMTS1, ADAMTS4, ADAMTS5, ADAMTS8, ADAMTS9), were reduced in HNSCC primary tumors compared with paired non-cancerous tissues (Demircan et al., 2009). Regarding tumor microenvironment ADAMTS15 expression is elevated in adjacent and margin tissue when compared with tumor center tissue (Stokes et al., 2010).

Breast cancer

Note

ADAMTS15 elevated expression correlates with favorable outcome in patients with breast cancer (Porter et al., 2006).

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This article should be referenced as such:

Cal S, Obaya AJ. ADAMTS15 (ADAM Metallopeptidase With Thrombospondin Type 1 Motif, 15). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(9):655-658.