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Gene Section
Review

ADAMTS9 (ADAM metallopeptidase with thrombospondin type 1 motif, 9)

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Abstract

Review on ADAMTS9, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

HGNC (Hugo): ADAMTS9

Location: 3p14.1

DNA/RNA

Description

The human ADAMTS9 gene is composed of 40 exons spanning a genomic region of about 172 kbp. The open reading frame of the coding region is 5808 bp.

Pseudogene

No pseudogene reported.

Protein

Description

ADAMTS9 is composed of a signal peptide, a propeptide, a metalloproteinase domain, a disintegrin-like domain, thrombospondin type 1-like repeats, a cystein-rich domain, a spacer domain, and a unique C-terminal domain (Somerville et al., 2003). A unique C-terminal domain was named as GON domain. The GON domain functions in the ER for protein transport from the ER to the Golgi (Yoshina et al., 2012). N-linked glycosylation of ADAMTS9 propeptide is found to be essential for ADAMTS9 secretion (Koo et al., 2007). ADAMTS9 is processed by furin extracellularly but not in the secretory pathway (Koo et al., 2006).

Following furin processing, mature ADAMTS9 is released from the cell surface (Koo et al., 2007).

ADAMTS9 is required for early mouse development. ADAMTS9 null mice die before gastrulation. ADAMTS9+/- mice develop anomalous eye such as corneal clouding, corneal neovascularisation, and adhesions of the lens and iris to the cornea (Koo et al., 2010).

Expression

ADAMTS9 is found in adult human ovary, pancreas, heart, kidney, lung, placenta, and skeletal muscle. ADAMTS9 is found in fetal brain, heart, kidney, lung, liver, skeletal muscle, spleen and thymus. According to northern blot analysis, the highest mRNA levels are found in heart, placenta, and skeletal muscle (Clark et al., 2000; Somerville et al., 2003).

ADAMTS9 is expressed in microvascular endothelial cells (Koo et al., 2010).

Following stimulation with TNFalpha, ADAMTS9 mRNA expression was enhanced in a human retinal pigment epithelial cell line (ARPE-19) (Bevitt et al., 2003). In a human chondrosarcoma cell line (OUMS-27) and human chondrocytes, exposure to IL-1 beta or TNF alpha upregulate ADAMTS9 mRNA expression (Demircan et al., 2005).

Induction of ADAMTS9 mRNA by IL-1beta was reported to occur via NFATc binding to the ADAMTS9 promoter in the OUMS-27 and in human chondrocyte (Yaykasli et al., 2009).

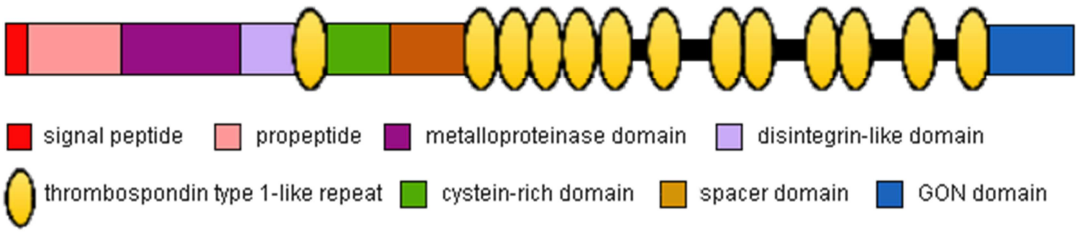

Diagram of the human ADAMTS9 protein.

In the human lung carcinoma epithelial cell line (A549), exposure to TGF- beta or IL-13 or Epstein-Barr virus infection led to enhanced ADAMTS9 mRNA expression. IL-4 exposure had no effect on the expression of ADAMTS9 in A549 (Keating et al., 2006).

Localisation

ADAMTS9 is present at the plasma membrane and the endoplasmic reticulum (Somerville et al., 2003; Yoshina et al., 2012).

Function

ADAMTS9 cleaves aggrecan and versican (Somerville et al., 2003). ADAMTS9 is involved in cell migration and inhibition of angiogenesis (Koo et al., 2010).
ADAMTS9 is implicated in the transport from the endoplasmic reticulum to the Golgi. This function is GON-domain dependent but protease activity independent (Yoshina et al., 2012).

Homology

ADAMTS9 and ADAMTS20 have the identical domain organization and exon structure and a similar primaly sequence. The unique C-terminal domain, GON domain, is highly similar in ADAMTS9 and ADAMTS20 (Somerville et al., 2003).

Mutations

Note
A downregulation of ADAMTS9 has been observed in some carcinoma that is induced by aberrant methylation of the gene.
The major C-risk allele of rs4607103 near ADAMTS9, conferring increased risk of type 2 diabetes.

Implicated in

Esophageal squamous cell carcinoma

Note
Complete loss or downregulation of ADAMTS9 gene expression was found in 15 out of 16 esophageal carcinoma cell lines. Promoter hypermethylation was involved in gene downregulation. Downregulation of ADAMTS9 was also found in primary esophageal tumor tissues from Hong Kong and from the high-risk region of Henan (Lo et al., 2007). Downregulation of ADAMTS9 expression led to tumorigenesis. Overexpression of ADAMTS9 induced suppression of tumor formation and angiogenesis in esophageal carcinoma cell line (Lo et al., 2010).

Nasopharyngeal carcinoma

Note
ADAMTS9 was downregulated in nasopharyngeal carcinoma cell lines. The mechanism of ADAMTS9 gene inactivation was attributed to promoter hypermethylation (Lung et al., 2008). Downregulation of ADAMTS9 expression led to tumorigenesis. Overexpression of ADAMTS9 induced suppression of tumor formation and angiogenesis in nasopharyngeal carcinoma cell line (Lo et al., 2010).

Colorectal cancer

Note
The frequency of ADAMTS9 promoter methylation in primary colorectal cancers was significantly higher than in normal tissues (Zhang et al., 2010).

Gastric cancer

Note
The frequency of ADAMTS9 promoter methylation in primary gastric cancers was significantly higher than in normal tissues (Zhang et al., 2010; Du et al., 2013). ADAMTS9 contributes to the suppression of tumorigenesis by decreasing cell proliferation, inducing cell apoptosis and inhibiting angiogenesis through regulating AKT/mTOR signaling pathway (Du et al., 2013).

Pancreatic cancer

Note
The frequency of ADAMTS9 promoter methylation in primary pancreatic cancers was significantly higher than in normal tissues (Zhang et al., 2010).

Type II diabetes

Note
Genome-wide assosiation studies (GWAS) linked a marker near the ADAMTS9 locus to type II diabetes (Zeggini et al., 2008). The major C allele

of rs4607103, located upstream of ADAMTS9, was established as a diabetes risk variant in GWAS. rs4607103 is associated with a decrease in insulin sensitivity of peripheral tissues (Boesgaard et al., 2009; Trombetta et al., 2013).

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