

Gene Section

Review

ADAM12 (ADAM metalloproteinase domain 12 (meltrin alpha))

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Published in Atlas Database: May 2008

Online updated version : <http://AtlasGeneticsOncology.org/Genes/ADAM12ID44084ch10q26.html>
DOI: 10.4267/2042/44442

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Identity

Other names: ADAM-12; MCMP; MCMPMltna; MLTN; MLTNA; Meltrin-alpha; Mltna

HGNC (Hugo): ADAM12

Location: 10q26.2

DNA/RNA

Description

Human ADAM-12L DNA spans 373186 bp and ADAM-12S DNA spans 347114 bp. Both sequences are composed of 19 exons.

Transcription

The full-length ADAM-12L cDNA spans 5048 nucleotides, including a 311- nucleotides 5'-untranslated region, an open reading frame of 2727 nucleotides encoding 909 aa, a TGA stop codon, and a 3'-untranslated region of 2006 nucleotides. Full-length ADAM-12S cDNA has a 2214 nucleotides open reading frame that is identical to ADAM-12L up to nucleotide 2426, whereupon it diverges. The final 102 nucleotides of the ADAM-12S open reading frame encode a 34-aa carboxyl terminus, followed by a TGA stop codon and a 3'-

end untranslated region of 788 nucleotides. The 3'-untranslated regions are different in the two human ADAM-12 forms.

Pseudogene

ADAM-12 seems to be encoded by a single copy gene which is located on chromosome 10q26. No pseudogenes reported.

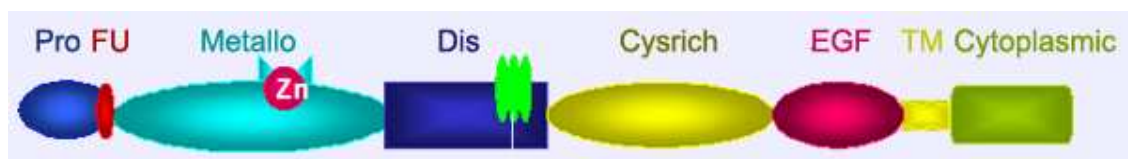
Protein

Note

Full-length ADAM-12L: 909 amino acids; Mr: 99,641. There are two isoforms of ADAM-12 resulting from an alternative splicing: mature membrane-bound ADAM-12 (ADAM-12L) (881 amino acids, Mr: 96,917) and a secreted form (ADAM-12S) (718 amino acids, Mr: 77,775).

Description

The open reading frame begins at the translation initiation codon ATG at nucleotide 312. Residues 1-28 encode the signal peptide. The mature human ADAM-12L contains 881 aa with an Mr of about 96,9 and that of ADAM-12S contains 718 aa with an Mr of 77,8. Five potential N-linked glycosylation sites are present.



Structure of ADAM proteinase. ADAM-12 is composed of a propeptide (Pro), a metalloproteinase (Metallo), a disintegrin (Dis), a cysteine-rich (Cysrich) domain followed by an EGF-like (EGF), a transmembrane (TM) and a cytoplasmic domain. ADAM-12 proteinase contains in addition a sequence recognized by furin-like enzymes (FU) (Rocks et al, 2008b).

These five sites are also found at the same position in mouse ADAM-12, whereas three additional sites present in mouse are not found in human ADAM-12. The human ADAM-12 metalloproteinase domain contains the highly conserved zinc-binding motif HEXGHXXGXXHD which is regulated by a potential "cysteine switch" in the prodomain.

Expression

Highly expressed in placenta and in lower amounts in skeletal muscle, heart, prostate, uterus, colon, small intestine, bladder, stomach. In prostate, uterus, colon, small intestine, bladder, stomach, the source of ADAM-12 may be the smooth muscle cells. ADAM-12 is also expressed by activated hepatic stellate cells (LePabic et al, 2003). ADAM-12 is present in higher amounts in maternal serum during pregnancy (Laigaard et al, 2006).

Localisation

Membrane-bound for ADAM-12L, extracellular localization for ADAM-12S.

Function

ADAM-12 is a catalytic active protein and functions ascribed to ADAM-12 in the literature are mostly related to its catalytic activity. Indeed, ADAM-12 is able to cleave Insulin-like Growth Factor Binding Protein-3 and -5 (IGFBP-3 and IGFBP-5). The release of increasing concentrations of bioavailable IGF through IGFBP cleavage is important during pregnancy for foetal growth (Laigaard et al, 2006). ADAM-12 is also able to cleave membrane-bound Heparin-binding EGF-like Growth Factor (HB-EGF) (Asakura et al, 2002).

Homology

Human version of ADAM-12 shares 84% overall amino acid identity with its mouse homolog. Homology is highest in cysteine-rich, metalloproteinase, and disintegrin domains and lower in the pro- and cytoplasmic domains. Human ADAM-12 shares about 83% with the rat homolog, 68% with zebra fish ADAM-12 and 99% with chimpanzees. Human ADAM-12 shares 45% overall amino acid similarity with ADAM-8, ADAM-9 and ADAM-15.

Mutations

Note

Three somatic mutations in ADAM-12 have been observed at significant frequencies in breast cancers (Dyczynska et al, 2008).

Somatic

D301H, G479E and L792F: the first two mutations involve highly conserved residues in ADAM-12 which inhibit its proteolytic processing and activation. These mutants are retained inside of the cell and are not transported to the cell surface (Dyczynska et al, 2008).

Implicated in

Lung cancer

Note

ADAM-12 mRNA and protein levels are elevated in biopsies of non small cell lung cancer compared to non cancerous lung tissues (Rocks et al, 2006).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

Contributes to enhance proliferation of bronchial epithelial cells through enhancement of membrane-bound HB-EGF shedding and activation of downstream HB-EGF/EGFR pathway. This cleavage also protects lung epithelial cells from etoposide-induced apoptosis (Rocks et al, 2008a).

Breast cancer

Note

Western Blots and immunoreactivity to ADAM-12 reveals that most of the malignant breast tissues exhibit ADAM-12 expression when compared to non-malignant breast lesions.

Prognosis

Urine of the majority of breast cancer patients is positive for ADAM-12 compared with urine from control patients in which ADAM-12 levels are significantly lower. Moreover, median levels of ADAM-12 in urine increase with disease progression (Roy et al, 2004).

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

Overexpression of ADAM-12 accelerates tumor development and increases tumor burden. ADAM-12 overexpressing tumours display lower tumor cell apoptosis and higher apoptosis rates in stromal cells (Kveiborg et al, 2005).

Bladder cancer

Note

ADAM-12 mRNA levels are upregulated in bladder cancer as determined by microarray analysis and RT-PCR as compared to control samples. ADAM-12 protein levels correlate with tumor stage and grade.

Prognosis

ADAM-12 levels are upregulated in urine of patients with bladder cancer compared with urine from healthy individuals. After removal of the tumor by surgery, levels of ADAM-12 in urine decrease. ADAM-12 is therefore an interesting biomarker of bladder cancer (Frohlich et al, 2006).

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

Not determined.

Hepatic cancer**Note**

Northern Blots show that ADAM-12 is expressed in human activated hepatic stellate cells. Hepatocellular carcinomas and liver metastases display higher ADAM-12 than normal liver and benign tumors. ADAM-12 expression is also correlated with tumor aggressiveness and progression (LePabic et al, Hepatology, 2003).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

ADAM-12 expression is induced by Transforming Growth Factor (TGF)- β in activated hepatic stellate cells through both PI3K/p70S6K and MEK/ERK pathways (LePabic et al, 2005).

Glioblastoma**Note**

Membrane-anchored ADAM-12 is overexpressed in glioblastomas compared to non-neoplastic brain tissues. In situ hybridization shows that glioblastoma cells are responsible for this gene expression (Kodama et al, 2004).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Oncogenesis

There is a relation between ADAM-12 mRNA

expression and proliferative activity of gliomas. This enhanced proliferation might be related to an increase of membrane-bound pro-HB-EGF shedding.

Intrauterine growth**Note**

ADAM-12 is able to cleave Insulin-like Growth Factor Binding Proteins (IGFBP) and thereby regulates the amount of free bioactive Insulin-like Growth Factor (IGF). The proposed role of ADAM-12 is the promotion of growth and development by breaking down IGFBPs, releasing IGF for uptake into cells to promote growth (Cowans et al, 2007).

Prognosis

In cases of poor foetal growth, Down syndrome, trisomy 18 pregnancies or in women who later develop preeclampsia, levels of ADAM-12 during early pregnancy are significantly lower than in normal pregnancies. The lower ADAM-12 levels result in less free IGF available for cell uptake and foetal growth promotion (Laigaard et al, 2005b; Laigaard et al, 2005a; Laigaard et al, 2003).

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Bone growth**Note**

ADAM-12S stimulates bone growth in ADAM-12S transgenic mice by modulating chondrocyte proliferation. Interestingly, the proteinase activity of ADAM-12 is necessary for the increased growth of bone tissues since mice expressing a truncated form of ADAM-12 lacking the pro- and metalloproteinase domains did not show an alteration in bone growth (Kveiborg et al, 2006).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

Adipogenesis and myogenesis**Note**

Involvement of ADAM-12 in adipogenesis and myogenesis through the shedding of membrane-bound HB-EGF (Kurisaki et al, 2003; Gilpin et al, 1998).

Prognosis

Not determined.

Cytogenetics

Not determined.

Hybrid/Mutated gene

Not determined.

Abnormal protein

Not determined.

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This article should be referenced as such:

Rocks N, Cataldo D. ADAM12 (ADAM metallopeptidase domain 12 (meltrin alpha)). *Atlas Genet Cytogenet Oncol Haematol*. 2009; 13(4):249-252.
