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Gene Section
Review

ADAM23 (ADAM metallopeptidase domain 23)

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Abstract

ADAM23 belongs to the ADAM (A Disintegrin And Metalloproteinase domain) family of proteins. Members of this family present a common structural organization including metalloprotease, disintegrin, cystein-rich, epidermal growth factor-like, transmembrane and cytoplasmatic domains and are structurally related to snake venom disintegrins. ADAM23 has close similarity to ADAM11 and ADAM22; is highly expressed in the CNS, and is crucial for normal brain development. Mice homozygous for an insertional mutation that inactivates the gene are smaller than normal littermates, show delayed lung development, are lethal by postnatal day 14, and display severe tremor and ataxia.
ADAM23 does not present metalloprotease activity and probably plays its biological role through the disintegrin domain. ADAM23 is involved in cell-cell adhesion and communication and cell-matrix modulation.
The ADAM23 gene is frequently silenced by DNA promoter methylation in different types of solid cancers and epigenetic inactivation is associated with cancer progression, increased tumor cell mobility and reduced tumor cell proliferation.

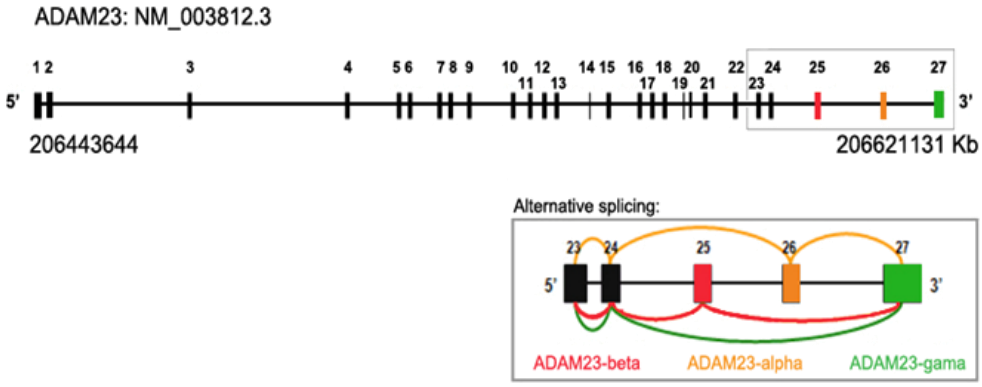
Keywords
ADAM family, cell-cell adhesion, cell migration, invasion, proliferation, differentiation, metastasis

Identity

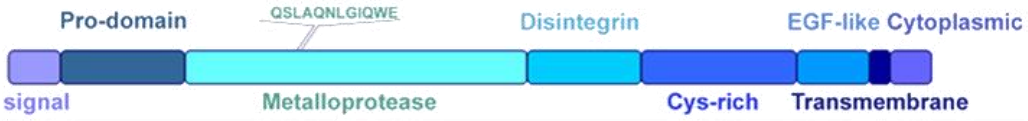
Other names: MDC3

HGNC (Hugo): ADAM23

Location: 2q33.3



Genomic structure of ADAM23 human gene composed of 27 coding exons. Black boxes represent constitutive exons present in all splicing isoforms. Colored boxes represent alternatively spliced exons.



Domain structure of ADAM23. Its deduced amino acid sequence lacks essential residues conserved in metalloproteinases (adapted from Cal et al., 2000).

DNA/RNA

Description

DNA contains 177488 bp composed of 27 coding exons (26 reported by RefSeq sequences).

Transcription

6236 bp mRNA transcribed (RefSeq NM_003812.3) in centromeric to telomeric orientation; 2499 bp open reading frame. There are three alternative splicing isoforms of the human ADAM23 gene: ADAM23-alpha (chosen as the 'canonical' sequence), ADAM23-beta and ADAM23-gamma. These splicing isoforms are generated by the mutually exclusive use or skipping of the exons 25 and/or 26, both of which coding for transmembrane domains with different aminoacid compositions. The ADAM23 proteins encoded by the alpha and beta splicing isoforms are anchored to the membrane by different transmembrane domains (encoded by exon 26 in the isoform alpha and by exon 25 in the isoform beta) and are predicted to have distinct membrane subdomain localizations. ADAM23-gamma is generated by exon skipping of exons 25 and 26 and therefore lacks the transmembrane domain and is predicted to be either a cytoplasmatic or a secreted isoform of the ADAM23 protein. ADAM23 mRNA is detected at high or medium expression levels in brain, testis and heart muscle (The Human Protein Atlas, ENSG00000114948).

Pseudogene

No pseudogenes reported.

Protein

Description

ADAM23 is a non-catalytically active member of ADAM family and exhibits all the conserved protein domains, including: an N-terminal signal, a pro-domain, a metalloprotease and a disintegrin domains, a cysteine-rich region, an EGF-like domain, a transmembrane and a short cytoplasmic domains. Within the metalloprotease domain, ADAM23 lacks the conserved zinc-binding sequence HEXXHXXGXXH, which is critical for the proteinase activity. Interacts with LGI1, LGI3 and LGI4 (leucine-rich glioma inactivated family), alphav-beta3 integrins and PrPc proteins.

Size: 832 amino acid; 92 kDa predicted (RefSeq NP_003803).

Expression

Detected at medium/high expression levels in 46 of 82 analyzed normal tissue types, including: brain, testis, lung, breast, colon, pancreas and kidney (according to The Human Protein Atlas).

Localisation

Cell membrane; single-pass type I membrane protein (isoform ADAM23-alpha and ADAM23-beta). Secreted protein (predicted for ADAM23-gama isoform).

Function

ADAM23 was originally described to promote neuroblastoma and astrocytoma cell-cell adhesion via direct interaction with alphavbeta3 integrin. Following reports showed that the interaction between ADAM23 and alphavbeta3 integrin inhibits cell-matrix adhesion and negatively modulates alphavbeta3 activation during metastatic progression. Silencing of the ADAM23 gene promotes cell cycle arrest and terminal differentiation in P19 mice embryonic carcinoma cells and, in MDA-MB435 and SK-Mel37 tumor cell lines, promotes tumor cell migration and invasion and inhibits tumor cell proliferation.

Homology

H. sapiens: ADAM23, P. troglodytes: ADAM23, C. lupus: LOC607871, M. musculus: ADAM23, R. novergicus: ADAM23, G. gallus: LOC424099.

Mutations

Note

No mutations have been reported for ADAM23 gene.

Germinal

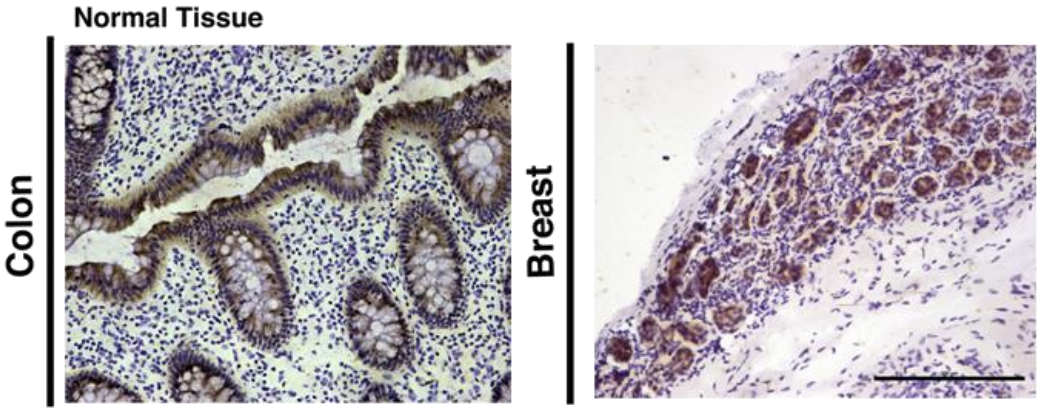
No germline mutations have been reported for the ADAM23 gene (OMIM603710).

Somatic

No somatic point mutations and CNVs have been reported.

Epigenetics

Epigenetic silencing of the ADAM23 have been frequently reported in different types of solid tumors.



Immunohistochemistry staining of ADAM23 protein in normal colon and normal breast tissues was carried out using the polyclonal antibody anti-ADAM23 (HPA012130, Sigma) (photograph courtesy of Dra. Gabriela F Barnabe from Ludwig Institute for Cancer Research - SP - Brazil).

Implicated in

Breast carcinoma

ADAM23 expression is downregulated by promoter hypermethylation during breast cancer progression and hypermethylation was significantly associated with a higher incidence of distant metastasis and reduced overall survival. Recently, ADAM23 epigenetic silencing during tumor progression was shown to generate genetic and functional heterogeneity in invasive breast tumors. ADAM23-intratumoral heterogeneity (ADAM23-ITH) was observed in topographically distinct areas of undifferentiated breast invasive ductal carcinomas, with invasive components being frequently composed by mosaic clusters of ADAM23-positive tumor cells coexisting in close proximity with ADAM23-silenced cells. Most importantly, it was demonstrated that ADAM23-ITH promotes tumor growth and metastasis by establishing a crosstalk between ADAM23-positives and ADAM23-negatives tumor cells in which ADAM23-negative cells promote tumor growth and metastasis by enhancing the proliferation and invasion of adjacent ADAM23-positive cells through the production of the ADAM23-ligant LGI4 (leucine-rich glioma Inactivated gene 4) and pro-migratory levels of nitric oxide (NO).

Lung carcinoma

ADAM23 protein levels is lower in non-small-cell lung carcinoma (NSCLC) compared to corresponding normal tissues and benign pulmonary lesions, and a decrease in ADAM23 protein expression was observed during NSCLC progression. Hypermethylation of ADAM23 promoter region was observed in 40% of NSCLC but in only 7.6% of the adjacent normal tissues.

Gastric tumors

ADAM23 promoter hypermethylation is frequently observed in gastric dysplasia (90%) and gastric tumors (29-55%) but is rarely observed in normal mucosa (9%). The frequency of ADAM23 methylation is higher in metastatic lesions compared to paired primary tumors. Homozygous loss of ADAM23 was also reported for gastric tumors but at a lower frequency (~3%).

Pancreatic tumors

ADAM23 promoter methylation was detected in 7 out of 24 (29%) primary invasive pancreatic ductal adenocarcinomas.

Head and neck cancer

ADAM23 promoter hypermethylation was detected in 18 out of 43 head and neck tumors (42%) and a significant association between ADAM23 hypermethylation and advanced stages (T3-T4) was observed larynx tumors.

Multiple myeloma

ADAM23 mRNA expression is absent in normal bone marrow plasma cells, but is aberrantly expressed in 2/131 (1,5%) patients with newly diagnosed multiple myeloma. In two independent cohorts of patients with primary multiple myeloma, 24 out of 557 patients (4%) showed increased levels of ADAM23 mRNA expression, which was significantly associated with poor overall survival.

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