

Gene Section Review

DMBT1 (deleted in malignant brain tumors 1)

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Published in Atlas Database: August 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/DMBT1ID309ch10q26.html>
DOI: 10.4267/2042/38489

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Identity

Hugo: DMBT1

Other names: gp-340 (glycoprotein-340; human); SAG (salivary agglutinin; human); apactin (mouse); CRP-ductin (mouse); gp300 (glycoprotein 300; mouse); muclin (mouse); vomeroglandin (mouse); ebnerin (rat); hensin (rabbit); BGM (bovine gallbladder mucin, cattle); H3 (rhesus monkey)

Location: 10q26.13

Local order: between D10S1421 and D10S1273E.

DNA/RNA

Description

The gene consists of 55 exons distributed over about 80

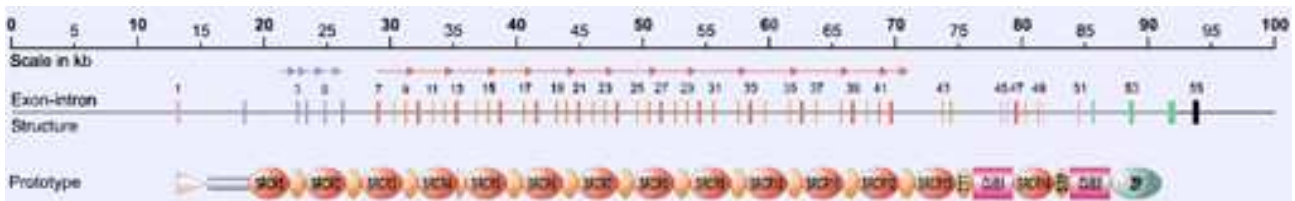
kb. Scavenger receptor cysteine-rich (SRCR) domains are coded by single exons. Two small exons coding for serine-threonine-proline-rich stretches of 20-24 amino acids in length follow each SRCR exon. To these stretches it has been referred to as SRCR-interspersed domains (SIDs). The only exception is that there is only one of the two SID exons between SRCR4 and SRCR5.

Transcription

Longest transcript identified so far: 7656 bp including 5'-utr, exons 1-16 and exons 18-54. Various alternative transcripts with variable numbers of SRCR and SID exons exist. Exon 55 has not yet been verified to be present in human transcripts.

Pseudogene

No pseudogene known so far.



Genomic organization of DMBT1. Top line: scale in kb. Second line: exon-intron structure of DMBT1 drawn to scale. Exons have the color code of the domains they are coding for. Exon 55 marked in black represents an exon with homology to the mouse and rat homologues, in which it codes for a transmembrane domain. Exon 55 has not yet been identified in a human transcript. Arrows depict regions, in which exon and intron sequences share high homologies. Bottom line: domain organization of the DMBT1 protein predicted from assembly of the first 54 exons. Entries to color codes and abbreviations are depicted in the section describing the protein.



Domain organization of DMBT1. Prototype: protein assembled from the first 54 exons (corresponding transcripts not yet identified). DMBT1/8kb.2: secreted DMBT1 variant encoded by the largest known transcript. DMBT1/6kb.1: secreted DMBT1 variant encoded by the smallest known transcript. Pink triangle: signal peptide putatively required for secretion; blue box repetitive motif of unknown function; red circles: scavenger receptor cysteine-rich (SRCR) domains; orange circles: SRCR-interspersed domains (SIDs); orange circles with TTT and STP: threonine- and serine-threonine-proline-rich domains with limited similarity to SIDs; CUB: C1r/C1s-Uegf-Bmp1 domains; ZP: zona pellucida domain.

Protein

Description

The largest known protein variant (DMBT1/8kb.2) comprises 2413 amino acids and has a calculated molecular weight of 265 kDa. Probably due to glycosylation the molecular weight of the purified protein is approximately 340 kDa. The smallest known variant (DMBT1/6kb.1), which lacks several SRCR domains and SIDs, comprises 1785 amino acids with a calculated molecular weight of 196 kDa. Various other protein variants lacking one or more SRCR domains may exist. The protein variants may arise due to genetic polymorphisms and/or alternative splicing.

The SRCR domains are involved in ligand interactions. An 11 amino acid motif (GRVEVLYRGSW) present in each of the repeated SRCR domains has been shown to be responsible for the binding of a broad spectrum of Gram-positive and Gram-negative bacteria. The N-terminal SRCR1/SD1 domain has been shown to interact with HIV gp120 and to suppress HIV infection. The functions of the CUB domains and of SRCR14, which shows only limited similarity to the other SRCR domains within DMBT1, have not yet been determined. In other proteins, ZP domains have been shown to function in oligomerization. DMBT1 is also secreted as high molecular weight oligomers.

SRCR, CUB, and ZP domains exclusively occur in multicellular animal organisms.

Expression

Main sites of DMBT1 expression are surface epithelial cells and associated glands, in particular in the respiratory and gastrointestinal tract. In most tissues low to moderate DMBT1 levels are expressed under normal conditions. An upregulation has been observed in response to various pathophysiological conditions, such as bacterial infection, inflammation, tumor-flanking tissues, carcinogen exposure, etc. Expression has also been noted in other tissues such as the brain and in immune cells.

Localisation

Extracellular. DMBT1 is either secreted to the mucus and other body fluids or to the extracellular matrix.

Function

DMBT1 exerts at least two distinct functions. As extracellular matrix protein, DMBT1 triggers polarity and terminal differentiation of epithelial cells as well as differentiation of embryonic stem cells to monolayered epithelia, which has been demonstrated by in vitro studies with rodent orthologs of DMBT1. DMBT1 secreted to the luminal side of epithelial surfaces plays a role in defense against bacterial and viral pathogens. This mechanism includes pathogen recognition through a peptide motif present in the SRCR domains and mediation of pathogen aggregation. DMBT1 further has been shown to exert anti-inflammatory effects. In response to activation of the intracellular pattern recognition molecule NOD2 and consecutive NF- κ B-activation, upregulation of DMBT1 takes place, which in turn hinders bacterial invasion and LPS-induced TLR4-activation. Hindrance of bacterial invasion may abolish NOD2 activation. Thus DMBT1 may act anti-inflammatory via inhibiting both NOD2- and TLR4-mediated NF- κ B-activation. As DMBT1 is NF- κ B responsive, this presumably builds up an autoregulatory homeostatic loop, by which DMBT1 is able to regulate its own expression as extracellular sensory element. These data point to a function in anti-inflammatory immune exclusion similar to mucosal antibodies (sIgA).

Homology

Homologies exist to other SRCR proteins such as CD5 and CD6, which function in immune defense. However, to date there is no SRCR protein known that additionally contains CUB and ZP domains. At the level of the SRCR domains, DMBT1 further shares some homologies with the sponge aggregation receptor (AR), which initiates the first steps in regeneration of a complete sponge body after dissociation.

Mutations

Germinal

Initial evidence has been gained that the SRCR- and SID-coding exons are subjected to copy number variations.

Somatic

Few point mutations have been identified in cancer so far. There is no hard evidence for an inactivation by biallelic mutation in cancer. Copy number variations of the SRCR- and SID-coding exons have been noted in different cancer types, including brain, lung, breast, gastrointestinal tumors and melanoma. It has not yet been determined to which extent these represent de novo rearrangements or germline mutations/polymorphisms. Underexpression has been observed for lung, colon, gastric, esophageal, breast, and skin cancer. By contrast overexpression was observed for pancreatic and prostate cancer.

Implicated in

Cancer

Disease

Based on underexpression and on its role in triggering differentiation, a role in tumor suppression of different cancer types, mainly of epithelial origin, has been proposed. A genetic scan in mice identified DMBT1 as candidate genetic modifier, which may determine the penetrance of breast cancer in the presence of p53 mutations. Lower DMBT1 protein levels have been observed in the normal mammary gland epithelium of women, which developed breast cancer versus tissues obtained from healthy donors.

Crohn's disease

Disease

Activation of DMBT1 was found to be impaired in the intestinal epithelium of Crohn's disease with predisposing NOD2 mutations.

Infection

Disease

Based on its broad bacterial binding specificity and inhibitory effects on bacterial and viral (HIV, influenza A viruses) infection in vitro, a role in infectious diseases has been proposed.

Caries

Disease

DMBT1 alias SAG (salivary agglutinin) has been studied for about two decades as the major caries bacteria agglutinating non-immunoglobulin in the saliva/oral cavity. Based on its capacity to aggregate caries bacteria (e.g. *Streptococcus mutans*), it was proposed to exert functions in preventing caries. Based on its capacity to mediate bacterial adhesion to enamel-like surfaces, it was proposed to exert functions in promoting caries by other groups.

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This article should be referenced as such:

Mollenhauer J, Poustka A. DMBT1 (deleted in malignant brain tumors 1). *Atlas Genet Cytogenet Oncol Haematol*. 2008;12(2):91-95.
