MMP19 (matrix metallopeptidase 19)

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Abstract

Review on MMP19, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: MMP18, RASI-1
HGNC (Hugo): MMP19
Location: 12q13.2

DNA/RNA

Description

MMP-19 can be found at chromosome 12q13.2 at location 56229214-56236767. The DNA sequence contains nine exons and eight introns, spanning 7.55 kb.

Alternative splicing results in multiple transcript variants for this gene (provided by RefSeq, Jan 2013). With reference to UniProtKB database, variant 1 represents the longest transcript and encodes isoform 1 (508 aa, 57 kDa, also known as RASI-1). Variant 2 encoded protein isoform 2 (222 aa, 25 kDa, also known as RASI-9). Variant 3 encoded protein isoform 3 (63 aa, 6 kDa, also known as RASI-6). Isoform 1 has been described as the canonical sequence and all the information described here, unless stated, refers to isoform 1.

Transcription

The MMP-19 promoter contains a TATA-box at position -29 and AP-1 binding site at position -73. Potential binding sites for other transcription factors such as NFkB, AP-2, and SP-1 also exist (Mueller et al., 2000).

Protein

Description

MMP-19 is a secreted protein. It contains a signal peptide for targeting to secretory vesicles. Like most secreted MMPs, MMP-19 is translated and secreted as catalytic inactive proproteins (zymogens), which needed to be activated by proteolytic cleavage of the propeptide region by other extracellular matrix (EMC) proteinases (Ra and Parks, 2007).
MMP-19 shares a typical MMP structural domain, containing the signal peptide, propeptide, catalytic domain, hinge region, and four hemopexin repeats (Pendás et al., 1997).

**MMP-19** is a zinc-dependent endopeptidase. The catalytic domain contains the active site for zinc ion binding and functions in catalytic activity such as substrate degradation. The hemopexin domain is responsible for substrate recognition (Ra and Parks, 2007). The catalytic activities of MMPs were reported to be regulated by tissue inhibitor of metalloproteinases (TIMPs). MMP-19 is reported to be strongly inhibited by TIMP-2, TIMP-3, and TIMP-4, and less efficiently by TIMP-1 (Clark et al., 2008).

**Expression**

MMP-19 was found to be expressed in a wide range of normal tissue types, such as nasopharyngeal epithelial cells, lung, breast, skin, intestine, pancreas, spleen, and ovary. MMP-19 was downregulated or lost during neoplastic progression in nasopharyngeal carcinoma (NPC), mammary gland tumor, skin neoplasm, intestine, and colon cancers (Pendás et al., 1997; Djonov et al., 2001; Impola et al., 2003; Bister et al., 2004; Chan et al., 2011).

**Localisation**

MMP-19 is located in the cytoplasm and secreted into the extracellular matrix.

**Function**

MMP-19 is a member of the MMP family of zinc-dependent endopeptidases. The catalytic domain responsible for degradation of various components of the ECM includes collagen type IV, nidogen-1, fibronectin, tenascin-C isoform, aggrecan, and laminin-5-gamma-2-chain (Stracke et al., 2000; Shiomi et al., 2010). MMP-19 is involved in many physiological activities such as cell proliferation, migration, and anti-angiogenesis.

**Implicated in Various cancers**

**Note**

Due to the ability of MMPs to degrade a variety of substrates, which may be involved in both cancer progression and repression, the role of MMP-19 in cancer development is as controversial as for all other MMPs. MMP-19 is reported to cleave insulin-like growth factor binding protein-3 (IGFBP-3), thereby causing the release of IGF-1 and enhanced human keratinocyte cell proliferation, migration, and adhesion on type I collagen (Sadowski et al., 2003). Also, MMP-19 was reported to process the laminin-5-gamma-2-chain in keratinocyte cells, which leads to the integrin switch favoring epithelial cell migration (Sadowski et al., 2005). On the other hand, a MMP-19 deficiency mouse model increased the onset of skin tumor invasion and vascularization, implicating the role of MMP-19 in inhibition of tumor invasion and anti-angiogenesis (Jost et al., 2006). The anti-angiogenic role of MMP-19 was demonstrated in the tube formation assay in human microvascular endothelial cells (HMEC-1). MMP-19 inhibited tube formation by degradation of nidogen-1, which is a scaffolding protein required for stabilizing new capillary formation (Titz et al., 2004). Further studies of MMP-19 on endothelial cells suggested other mechanisms of MMP-19 in inhibition of angiogenesis. MMP-19 digests plasminogen to generate angiostatin-like fragments, which are antagonists of angiogenesis and inhibit migration and proliferation of endothelial cells (Brauer et al., 2011).

Functional studies of MMP-19 demonstrated its tumor suppressive and anti-angiogenesis functions in nasopharyngeal carcinoma (NPC). MMP-19 reduces colony-forming ability of NPC cells and suppresses tumor formation in nude mice. Also, MMP-19 reduces tube-forming ability in human umbilical vein endothelial cells (HuVEC) and human microvascular endothelial cells (HMEC-1). The anti-angiogenic activity of MMP-19 in NPC is associated with reduction of secreted vascular endothelial growth factor (VEGF) in the conditioned media (Chan et al., 2011). Recent study in NPC cells demonstrated MMP-19 increased cisplatin sensitivity through production of γ-H2AX.
and attenuation of NER activity to repair cisplatin-induced DNA damage, therefore increasing the cisplatin-induced apoptosis in NPC (Liu et al., 2013).

**Rheumatoid arthritis (RA)**

**Note**

MMP-19 was first isolated as an autoantigen from the synovium of a rheumatoid arthritis patient suggesting its role in RA-associated joint tissue destruction (Sedlacek et al., 1998).

**References**


This article should be referenced as such: