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Gene Section

Review

SPINT1 (serine peptidase inhibitor, Kunitz type 1)

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Identity

Other names: HAI; HAI-1; HAI1; MANSC2

HGNC (Hugo): SPINT1

Location: 15q15.1

DNA/RNA

Description

The human SPINT1 gene spans approximately 13.6 kb in length and consists of 11 exons separated by 10 introns. The size of the exons ranges from 26 bp (exon 6) to about 0.8kb (exon 11). The size of introns ranges from 83 bp to about 7 kb. The first exon encodes only a part of 5'-untranslated region (UTR) of the SPINT1 transcript. Exon 2 contains the remaining 5'-UTR and the putative signal sequence. Two Kunitz-type inhibitor domains (KD-1 and KD-2) are encoded by exons 5 and 9, respectively.

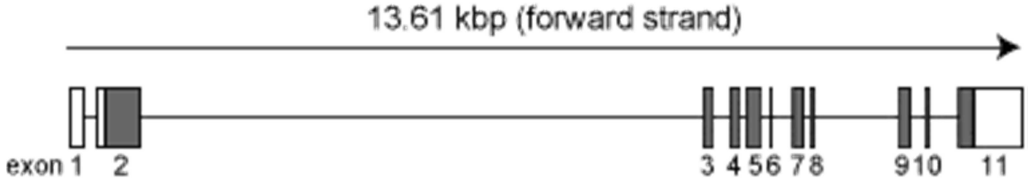
Transcription

There are two major transcripts, isoform 1 (also known as HAI-1B) and isoform 2 (also known as HAI-1 or HAI-1A) produced by alternative splicing. Isoform 1 and isoform 2 mRNAs encode for 529 and 513 amino acids, respectively.

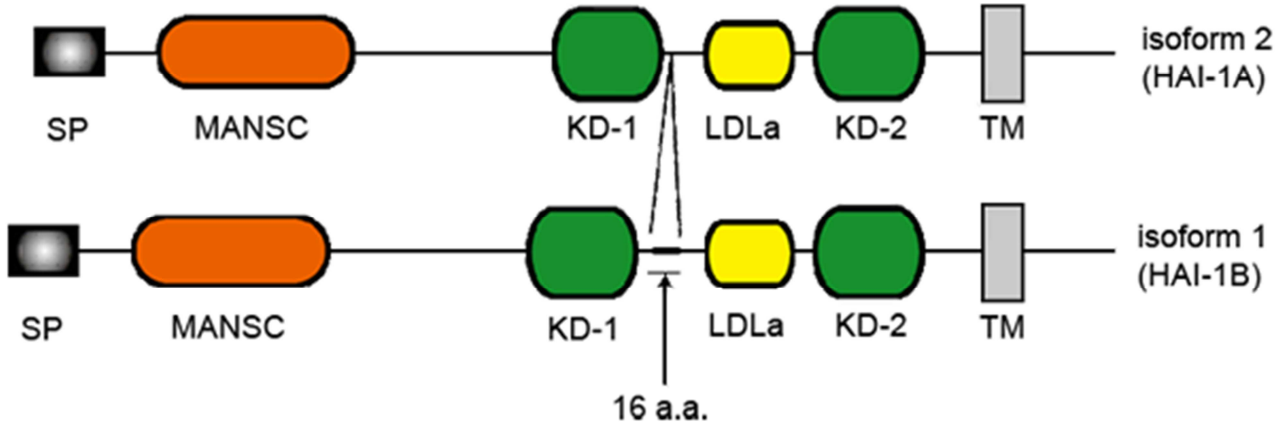
Protein

Description

The protein encoded by this gene is a member of the Kunitz family of serine proteinase inhibitors. Shimomura et al. (1997) purified this protein from a conditioned medium of a gastric carcinoma cell line MKN45 as a potent inhibitor specific for hepato-cyte growth factor activator (HGFAC), a serum serine proteinase that is thought to be involved in the proteolytic activation of hepatocyte growth factor (HGF) in injured tissues. For this reason, SPINT1 was initially designated as HGFAC inhibitor type 1 (HAI-1). The initially cloned cDNA of SPINT1 encoded a 513 amino acids protein (478-amino acid mature protein with a calculated molecular mass of 53.3 kD). SPINT1 is a trans-membrane protein expressed on the cell surface. It is composed of an extracellular domain containing an N-terminal Kunitz domain (KD1), a low-density lipoprotein (LDL) receptor-like domain and a C-terminal Kunitz domain (KD2), followed by a transmembrane region and a short cytoplasmic domain. Later, a major transcript variant, also known as HAI-1B, was reported by Kirchhofer et al. (2003).



Structure of the human SPINT1 gene.



Structures of SPINT1 protein isoform 1 (HAI-1B) and isoform 2 (HAI-1A). SP, signal peptide; MANSC, motif at N terminus with seven cysteines; KD-1, Kunitz domain-1; LDLa, low-density lipoprotein receptor domain class A; KD-2, Kunitz domain-2; TM, transmembrane domain. Isoform 1 (HAI-1B) contains an extra 16 amino acids adjacent to the C terminus of KD-1.

This variant encodes the longer isoform consisting of an extra 16 amino acids adjacent to the C terminus of Kunitz domain-1 (KD1); however, there is no functional difference between HAI-1 (HAI-1A) and HAI-1B. Previous studies demonstrated that SPINT1 potently inhibits the action of a variety of trypsin-like serine proteinases, some of which may be involved in carcinogenesis, invasion and metastasis. These proteinases include HGFAC, matriptase/ST14, hepsin/TMPRSS1 and human kallikrein 1-related peptidases such as KLK4 and KLK5. Among them, matriptase/ST14 and hepsin/TMPRSS1 belong to the type II trans-membrane serine protease superfamily. Other possible target proteinases include prostasin/PRSS8 and trypsin. Evidence suggests that matrip-tase/ST14 is the most important cognate proteinase of SPINT1 on epithelial surface. KD-1 is respon-sible for the inhibition of two major target proteinases, matriptase/ST14 and HGFAC.

Expression

SPINT1 protein is strongly expressed in the surface epithelium of gastrointestinal tracts, endocervical epithelium, ductal epithelia of biliary tracts and pancreas, prostatic glandular epithelium and renal tubular epithelium. It is also strongly expressed in hair cortex and cuticle cells, and to a lesser degree in epidermal keratinocytes. Mesothelial cells on the serous surface also express SPINT1. Weaker expression has been detected in the endothelial cells of capillaries, venules and lymphatics. Placental tissue shows very high level of SPINT1 mRNA, and villous cytotrophoblasts are mainly responsible for this expression.

Localisation

SPINT1 is mainly located on the basolateral membrane of polarized epithelial cells.

Function

To date, several proposed functions of SPINT1 have been reported.

Inhibition of serine proteinases: SPINT1 strongly inhibits HGFAC, trypsin, KLK4, KLK5, matriptase/ST14, prostasin/PRSS8 and hepsin/ TMPRSS1.

Optimal regulation of pericellular proteinase activity: Evidence has suggested that SPINT1 is required for the trafficking of proforms of matriptase/ST14 to the cell surface and also for the activation of pro-matriptase/ST14 even though it can inhibit matriptase/ST14 activity. Therefore, without SPINT1, activation and proper localization of matriptase/ST14 appear to be significantly impaired. Such paradoxical effects of SPINT1 are also observed in the interaction with HGFAC. SPINT1 inhibits HGFAC, but paradoxically, serves as a reservoir of active HGFAC on the cell surface.

Regulation of pericellular HGF activation: Among target proteinases of SPINT1, HGFAC, matriptase/ ST14 and hepsin/TMPRSS1 are known to activate precursor form of HGF (proHGF). Thus, SPINT1 is thought to regulate pericellular proHGF activation.

Function in the placenta development: SPINT1 is essential in the placental development, as SPINT1-deficient mouse embryos die during mid-gestation due to impaired formation of the placental labyrinth layer.

Function in the skin development: Rescue of the placental function results in successful delivery of SPINT-1-deficient neonates. However, they die within 16 days after delivery with significant skin abnormalities such as abnormal keratinization and impaired formation of hair cuticle. Therefore, SPINT1 is critical in the regulated keratinization of epidermis and formation of hair cuticle.

Tumor suppressor activity: Transgenic over-expression of matriptase/ST14 resulted in skin carcinogenesis. However, the development of skin cancer (squamous cell carcinoma) was suppressed when SPINT1 was co-expressed.

Homology

SPINT-2 (also known as HAI-2 or placental bikunin) is also a membrane-bound Kunitz-type serine proteinase inhibitor consisting of two extracellular Kunitz domain. The amino acids identity between SPINT1 KD-1 and SPINT2 KD-1 is 54%, and between SPINT1 KD-2 and SPINT2 KD-2 is 36 %. However, SPINT2 lacks MANSC domain and LDL receptor-like domain.

Implicated in

Various cancers

Oncogenesis

A possible tumor suppressor activity of SPINT1 has been reported in matriptase/ST14-induced skin carcinogenesis. Immunohistochemical studies suggest that the balance between SPINT1 and its target proteinase such as matriptase/ST14 may be important in the progression of breast cancer and prostate cancer. Downregulation of SPINT1 is also reported in part of the colon, renal cell and ovarian carcinoma cases. In vitro knockdown of SPINT1 results in an invasive phenotype of certain epithelial and carcinoma cells.

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