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Gene Section
Mini Review

SPAM1 (sperm adhesion molecule 1 (PH-20 hyaluronidase, zona pellucida binding))

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Identity

Other names: EC 3.2.1.35, HYA1, HYAL1, HYAL3, HYAL5, Hyal-PH20, MGC26532, PH-20, PH20, SPAG15

HGNC (Hugo): SPAM1

Location: 7q31.32

Local order: According to NCBI Map Viewer, genes flanking SPAM1 in centromere to telomere direction on 7q31.3 are:
- HYALP1 7q31.3 hyaluronoglucosaminidase pseudogene 1
- HYAL4 7q31.3 hyaluronoglucosaminidase 4
- SPAM1 7q31.3 sperm adhesion molecule 1
- TMEM229A 7q31.32 transmembrane protein 229A
- hCG_1651160 7q31.33 SSU72 RNA polymerase II CTD phosphatase homolog pseudogene

Note: SPAM1 is a glycosyl-phosphatidyl inositol (GPI)-anchored enzyme found in all mammalian spermatozoa. The protein has a hyaluronidase activity that enables sperm to penetrate the cumulus, a role in zona pellucida binding and also participates in Ca^{2+} signaling associated acrosomal exocytosis.

DNA/RNA

Note
The human genome contains six hyaluronidase like genes. Three of them (HYAL1, HYAL2 and HYAL3) are clustered on chromosome 3p21.3 and the other three (HYAL4, SPAM1 and HYALP1) are clustered on chromosome 7q31.3. Of the three genes on chromosome 7q31.3, HYALP1 is an expressed pseudogene. The extensive homology between the six hyaluronidase genes suggests an ancient gene duplication event before the emergence of modern mammals.

Description

According to Entrez Gene, SPAM1 gene maps to locus NC_000007 and spans a region of 46136 bp. According to Spidey (mRNA to genomic sequence alignment tool), SPAM1 has 7 exons, the sizes being 78, 112, 1160, 90, 441, 99 and 404.

Transcription

The SPAM1 mRNA has two isoforms; transcript variant 1 (NM_003117) a 2395 bp mRNA and transcript variant 2 (NM_153189) a 2009 bp mRNA. The variant 2 uses an alternate in-frame splice site in the 3' coding region, compared to variant 1, resulting in a shorter C-terminus.
The promoter region of SPAM1 has been shown to contain a CRE (cAMP-responsive element) sequence which is a binding site for CREM (cAMP-responsive element modulator) and thus Spam1 is under a cAMP-dependent transcriptional regulation. No TATA or CCAAT boxes were found in the promoter region of SPAM1.



The diagram of SPAM1 transcript variant 1. The red boxes represent the exons (in scale) and exon numbers are given below the boxes.

The testis-specific promoters of the human and mouse SPAM1 genes are derived from a sequence that was originally part of an ERV pol gene.

Pseudogene

The human SPAM1 pseudogene HYALP1 is located on chromosome 7q31.3.

Protein

Note

Two sperm adhesion isoforms exist; one is 511 aa long isoform 1 and the other 509 aa long isoform 2. When the two isoforms are aligned the sequences are 100% identical and no functional difference has been reported.

Description

SPAM1 is a 68 kDa protein that belongs to glycosyl hydrolase 56 family. This family of enzymes has hyaluronidase activity which hydrolyses the glycosidic bond between two or more carbohydrates, or between a carbohydrate and a non-carbohydrate moiety. Sperm hyaluronidase is active at neutral and acidic pHs which results from different active sites in the hyaluronidase domain at the N-terminus of the protein. The hyaluronidase domain also contains a hyaluronic acid (HA) binding site that plays a role in the signaling pathway leading to acrosomal exocytosis. The protein also contains a zona binding domain at the C-terminal end.

Expression

According to GNF Expression Atlas 2 Data from U133A and GNF1H Chips, SPAM1 expression is widely limited to testis and epididymis but it was also found to be expressed in murine kidney and female reproductive tract. Both rare and abundant SPAM1 transcripts have been found in neoplastic breast tissue and in a number of other cancers including pharyngeal astatic melanomas and gliomas. In normal somatic cells rare transcripts have been found in breast tissue and in fetal, placental, and prostate cDNA libraries.

Localisation

SPAM1 is located on the sperm surface and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. The acrosomal membrane SPAM1 differs biochemically from the one on the sperm surface.

Function

SPAM1 is a multifunctional protein; a hyaluronidase that acts in penetrating the cumulus, a receptor for hyaluronic acid induced cell signaling which leads to acrosomal exocytosis and a receptor for the zona pellucida surrounding the oocyte. The zona pellucida recognition function is ascribed to the inner acrosomal membrane SPAM1. The neutral enzyme activity of plasma membrane SPAM1, which is GPI anchored, is responsible for local degradation of the cumulus ECM during sperm penetration. Plasma membrane SPAM1 mediates HA-induced sperm signaling via the HA binding domain. SPAM1 is also secreted by the epithelial cells of the epididymis and has a role in sperm maturation. In addition SPAM1 is implicated in fluid reabsorption and urine concentration in kidney.

Homology

- Pan troglodytes sperm adhesion molecule 1 (SPAM1)
- Canis lupus familiaris sperm adhesion molecule 1 (SPAM1)
- Bos taurus sperm adhesion molecule 1 (SPAM1)
- Mus musculus hyaluronoglucosaminidase 5 (Hyal5)
- Mus musculus sperm adhesion molecule 1 (SPAM1)
- Rattus norvegicus sperm adhesion molecule 1 (HYALP_RAT)
- Gallus gallus sperm adhesion molecule 1 (SPAM1)
- Danio rerio sperm adhesion molecule 1 (Spam1)

Mutations

Note

According to dbSNP, one validated missense SNP for SPAM1 is found in the 47th aa position causing a V to A (rs34633019) substitution. Other SNPs causing synonymous changes are: rs34404662 A/G substitution at the 3rd amino acid residue (Val), rs2285996 A/G substitution at the 184th amino acid residue (Lys) and rs34978112 C/T substitution at the 330th amino acid residue (Ala). No clinical associations with these SNPs have been reported.

Germinal

In mice bearing Robertsonian translocation Rb(6.15) and (6.16), reduced Spam1 hyaluronidase activity was found to cause sperm dysfunction. It was proposed that entrapment of spontaneous Spam1 mutations, owing to recombination suppression near the Rb junctions was the major effect.

According to in vitro mutagenesis experiments the following mutations were detected to have functional consequences:

- D146N: 80% loss of activity
- E148Q: loss of activity
- R211G: 90% loss of activity
- E284Q: loss of activity
- R287T: loss of activity

Implicated in

Breast cancer

Oncogenesis

Increased levels of SPAM1 are noted in invasive and metastatic breast cancer compared to ductal carcinoma in situ (DCIS). Tumors from African American women with invasive and metastatic breast cancer showed higher levels of SPAM1 than Caucasians. Varying levels of SPAM1 in mammary

tissue may contribute to early invasion and metastasis of breast cancer.

Laryngeal cancer

Oncogenesis

SPAM1 expression was found to be significantly elevated in primary laryngeal cancer tissue and even higher in metastatic lesions compared with normal laryngeal tissue. SPAM1 may therefore be a useful tumor marker and prognostic tool for laryngeal cancer. In squamous cell laryngeal carcinoma aberrant expression of SPAM1 at late stages of cancer was detected.

Colon Cancer

Oncogenesis

SPAM1 mRNA was present in mRNA from four biopsies obtained from patients with colorectal cancers. Normal colonic mucosal tissues obtained from the same patients did not express SPAM1 mRNA. In metastatic colon carcinoma cell lines but not in non-metastatic cell lines, SPAM1 expression was detected. Strong angiogenesis developed in four of five animals injected with $SPAM1^+$ colon carcinoma VAC05 cells. However, only one of five animals injected with $SPAM1^-$ VAC06 cells developed significant angiogenesis.

Melanoma

Oncogenesis

SPAM1 expression is seen in metastatic melanoma but not in non-metastatic melanoma cell lines (SMMU-2 and SMMU-1 respectively). $SPAM1^+$ human melanoma cell line SMMU-2 but not $SPAM1^-$ SMMU-1 cells induced angiogenesis in mice cornea although the exact mechanisms of how SPAM1 induces angiogenesis is not known.

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