

Gene Section

Mini Review

HYAL1 (hyaluronoglucosaminidase 1)

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Identity

Hugo: HYAL1

Other names: EC 3.2.1.35; HYAL-1; NT6; LUCA1; LUCA-1; FUS2; Hyaluronidase-1 precursor; Hyaluronoglucosaminidase-1; Hs.75619; MGC45987

Location: 3p21.3

Local order: The gene of Hyal1 is tightly clustered with HYAL-2 and HYAL-3. The gene for Hyal-2, HYAL2, the earliest known lysosomal hyaluronidase, resides immediately centromeric to HYAL1.

Note: The HYAL1 gene was identified as identical with LUCA-1, a candidate tumour suppressor gene, especially for tobacco-related cancers.



DNA/RNA

Description

The HYAL1 gene contains three exons and spans 12,492 bases (start: 50,312,324 bp to end 50,324,816 from 13pter) oriented at the minus strand.

Transcription

Eight alternatively spliced transcript variants of this gene encoding six distinct isoforms have been described. The longest transcript has a length of 2,518 bps, however it is not translated to protein, since, by retaining intron 1 (occurring within exon 1), it has a number of stop codons. The longest transcript that produces active HYAL1 has a length of 2075 bps.

Localisation

It is a secreted enzyme found in plasma and it is also present in lysosomes.

Pseudogene

PHYAL1.

Protein

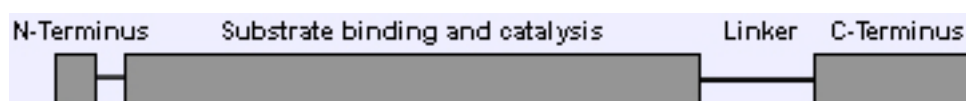
Note: HYAL1 is a secreted somatic tissue hyaluronidase, and the predominant hyaluronidase in human plasma. Although HYAL1 is predominantly secreted, it has an acid pH optimum in vitro. HYAL1 can degrade high molecular weight hyaluronan to small oligomers, primarily to tetrasaccharides, whereas HYAL2 (the other major human hyaluronidase) high molecular mass hyaluronan to an approximately 20 kDa product (approximately 50 saccharide units).

Description

Size: 435 amino acids; Molecular mass: 48368 Da. The enzyme belongs to the group of carbohydrate-active enzymes (<http://www.cazy.org/CASy>), termed glycosyl hydrolase 56 family.

Expression

HYAL1 is highly expressed in liver, kidney and heart and weakly expressed in lung, placenta and skeletal muscle. No expression is detected in adult brain. Isoform 1 is expressed only in bladder and prostate cancer cells, G2/G3 bladder tumor tissues and lymph node specimens showing tumor invasive tumors cells. Isoform 3, isoform 4, isoform 5 and isoform 6 are expressed in normal bladder and bladder tumor tissues. HYAL1 expression has been described in squamous cell carcinoma, in small cell lung cancer and glioma lines.



Function

It is a hydrolytic enzyme (endo-beta-acetyl-D-hexosaminidase) with optimum pH about 3.7, acting on hyaluronan, chondroitin and chondroitin sulphate. It possesses also transglycosidase activity using hyaluronan and chondroitin sulphate or chondroitin as substrates. This reaction is not well understood, and the precise enzymatic mechanism is not known.

Homology

The enzyme possesses 70-80% homology to orthologue hyaluronidases, 40% homology to paralogous hyaluronidases of the human and high homology with HYAL1 of other species.

Mutations

Somatic

There are not extended reports regarding mutations of HYAL1 gene. The patient with hyaluronidase deficiency was a compound heterozygote for two mutations in the HYAL1 gene: a 1412G-A mutation that introduced a nonconservative amino acid substitution (glu268 to lys) in a putative active site residue, and a complex intragenic rearrangement, 1361del37ins14, that resulted in a premature termination codon. In addition, the mutated HYAL1 gene has a markedly different expression pattern than the normal one.

Implicated in

Mucopolysaccharidosis type IX (MPS9)

Note: Defects in HYAL1 are the cause of mucopolysaccharidosis type IX, also called hyaluronidase deficiency.

Disease

The clinical features are periarticular soft tissue masses, mild short stature and acetabular erosions, absence of neurological or visceral involvement and high hyaluronan concentration in the serum.

Cancer

Note: HYAL1 is inactivated in most lung cancers in a conventional manner, by loss of heterozygosity or by homozygous deletion, at the DNA level. It is also inactivated in many head and neck carcinomas that are tobacco-related by aberrant splicing of the mRNA, so that only the nontranslatable form is transcribed. In addition, the expression of an alternative spliced isoform resulting in active enzyme may negatively regulate bladder tumor growth, infiltration, and angiogenesis. On the other hand, HYAL1 can function as oncogene in many cancers of the prostate and urinary tract and seems to play important role in squamous cell laryngeal carcinoma.

References

- Csóka AB, Frost GI, Wong T, Stern R. Purification and microsequencing of hyaluronidase isozymes from human urine. *FEBS Lett* 1997;417:307-310.
- Frost GI, Csóka AB, Wong T, Stern R. Purification, cloning, and expression of human plasma hyaluronidase. *Biochem Biophys Res Commun* 1997;236:10-15.
- Csóka AB, Frost GI, Heng HH, Scherer SW, Mohapatra G, Stern R. The hyaluronidase gene HYAL1 maps to chromosome 3p21.2-p21.3 in human and 9F1-F2 in mouse, a conserved candidate tumor suppressor locus. *Genomics* 1998;48:63-70.
- Lepperdinger G, Strobl B, Kreil G. HYAL2, a human gene expressed in many cells, encodes a lysosomal hyaluronidase with a novel type of specificity. *J Biol Chem* 1998;273:22466-22470.
- Csóka AB, Scherer SW, Stern R. Expression analysis of six paralogous human hyaluronidase genes clustered on chromosomes 3p21 and 7q31. *Genomics* 1999;60:356-361.
- Triggs-Raine B, Salo TJ, Zhang H, Wicklow BA, Natowicz MR. Mutations in HYAL1, a member of a tandemly distributed multigene family encoding disparate hyaluronidase activities, cause a newly described lysosomal disorder, mucopolysaccharidosis IX. *Proc Natl Acad Sci USA* 1999;96:6296-6300.
- Frost GI, Mohapatra G, Wong TM, Csóka AB, Gray JW, Stern R. HYAL1LUC1, a candidate tumor suppressor gene on chromosome 3p21.3, is inactivated in head and neck squamous cell carcinomas by aberrant splicing of pre-mRNA. *Oncogene* 2000;19:870-877.
- Lerman MI, Minna JD. The 630-kb lung cancer homozygous deletion region on human chromosome 3p21.3: identification and evaluation of the resident candidate tumor suppressor genes. *Cancer Res* 2000;60:6116-6133.
- Csóka AB, Frost GI, Stern R. The six hyaluronidase-like genes in the human and mouse genomes. *Matrix Biol* 2001;20:499-508. (Review).
- Lokeshwar VB, Schroeder GL, Carey RI, Soloway MS, Iida N. Regulation of hyaluronidase activity by alternative mRNA splicing. *J Biol Chem* 2002;277:33654-33663.
- Shuttleworth TL, Wilson MD, Wicklow BA, Wilkins JA, Triggs-Raine BL. Characterization of the murine hyaluronidase gene region reveals complex organization and cotranscription of Hyal1 with downstream genes, Fus2 and Hyal3. *J Biol Chem* 2002;277:23008-23018.
- Junker N, Latini S, Petersen LN, Kristjansen PE. Expression and regulation patterns of hyaluronidases in small cell lung cancer and glioma lines. *Oncol Rep* 2003;10:609-616.
- Jedrzejas MJ, Stern R. Structures of vertebrate hyaluronidases and their unique enzymatic mechanism of hydrolysis. *Proteins* 2005;61:227-238.
- Lokeshwar VB, Cerwinka WH, Isoyama T, Lokeshwar BL. HYAL1 hyaluronidase in prostate cancer: A tumor promoter and suppressor. *Cancer Res* 2005;65:7782-7789.
- Christopoulos TA, Papageorgakopoulou N, Theocharis DA, Mastronikolis NS, Papadas TA, Vynios DH. Hyaluronidase and CD44 hyaluronan receptor expression in squamous cell laryngeal carcinoma. *Biochim Biophys Acta* 2006;1760:1039-1045.
- Lokeshwar VB, Estrella V, Lopez L, Kramer M, Gomez P, Soloway MS, Lokeshwar BL. HYAL1-v1, an Alternatively Spliced Variant of HYAL1 Hyaluronidase: A Negative Regulator of Bladder Cancer. *Cancer Res* 2006;66:11219-11227.

Stern R, Jedrzejas MJ. Hyaluronidases: their genomics, structures, and mechanisms of action. *Chem Rev* 2006;106:818-839. (Review).

Chao KL, Muthukumar L, Herzberg O. Structure of human hyaluronidase-1, a hyaluronan hydrolyzing enzyme involved in tumor growth and angiogenesis. *Biochemistry* 2007;46:6911-6920.

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