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Gene Section
Mini Review

CSTB (cystatin B (stefin B))

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Identity

Other names: CPI-B; CST6; Cystatin-B; EPM1; PME; STFB; Stefin-B

HGNC (Hugo): CSTB

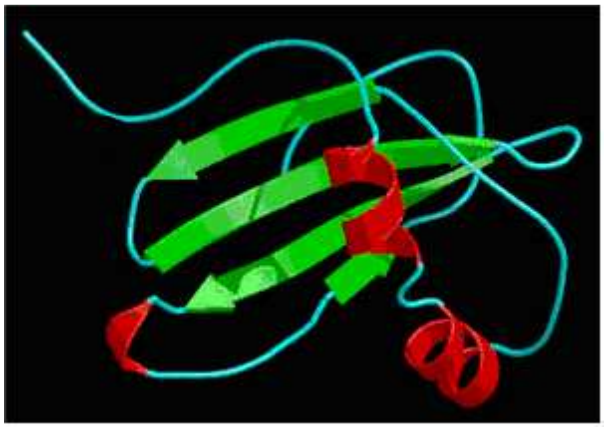
Location: 21q22.3

DNA/RNA

Description

The stefin B gene is located on human chromosome 21q22.3 and it contains 3 exons and 2 introns. The transcript length of stefin B mRNA is 294 bps. A novel variant, with retention of the entire intron 2 is transcribed from two exons with an ORF of 249 bp. It encodes a putative 9.0-kDa protein of 83 amino acids, including 57 identical to stefin B followed by 26 amino acids encoded by the intron 2 sequences.

Protein



Richardson diagram of stefin B structure: alpha-helixes are shown in red and beta-sheets in green (MEROPS: the peptidase database - I25.003: cystatin B).

Description

The cystatin superfamily comprises at least four families of closely related proteins, such as stefins (family I), cystatins (family II), kininogens (family III), and various structurally related but noninhibitory proteins of family IV. A significant structural difference between stefins and cystatins is the signal peptide, which is responsible for extracellular targeting of cystatins, whereas stefins lack this peptide and have been reported as intracellular inhibitors. Human stefin B is a single chain protein consisting of 98 amino acid residues, with a molecular mass of 11,175 kDa. Stefin B is a neutral protein with pI values between 5.9 - 6.5 and is able to form a dimmer stabilized by noncovalent forces. Like other members of the cystatin superfamily, stefin B is reversible and competitive inhibitor of cysteine proteases, particularly cathepsin L and cathepsin S with Ki values in the picomolar range whereas cathepsin B inhibition is weaker (Ki 10^{-7}M).

Expression

Stefin B is widely distributed among different cell types and tissues. Although it lacks an export signal sequence and is generally thought to function intracellularly, it has also been found in extracellular fluid.

Function

Stefin B is thought to play a role in protecting cytosolic and cytoskeleton proteins against the cysteine proteases accidentally released from lysosomes. Besides protease inactivation stefin B could bind other proteins in a multiprotein complex which might contribute to the disease in patients with progressive myoclonus epilepsy. Decreased levels of stefin B mRNA were detected in patients with progressive myoclonus epilepsy and associated with excessive activity of cathepsin B. Moreover, stefin B may be important in

the control of osteoclasts bone resorption. It inhibits bone resorption by down-regulating intracellular cathepsin K activity. On the other hand stefin B protected osteoclasts from experimentally induced apoptosis, promoting cell survival in the nervous system.

Homology

Human stefin B exhibit a high degree of homology to other cysteine protease inhibitors of the cystatin superfamily which includes human stefin A and the homologues in other species. It is 79% identical with cystatin beta from rat liver, but contains only a single cysteine.

Mutations

Note

Eight mutations in the stefin B gene have been reported to associate with an autosomal recessive neurodegenerative disorder, progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1). Most of the disease alleles harbour an unstable expansion of at least 30 copies of a normally polymorphic 12-nucleotide, dodecamer repeat located in the promoter region of the stefin B gene. Three reported EPM1 mutations affect splice sites, two result in amino-acid changes and two predict truncated proteins either through creating a stop codon or producing a frameshift.

Implicated in

Invasive cancers

Disease

Higher levels of stefin B in tumours have been determined in lung, breast, head and neck and prostate cancer as well as in murine lymphosarcomas, hepatomas and Lewis lung carcinomas. These higher levels, up to a certain level, may counter-balance the excessive activity of cysteine cathepsins, associated with matrix remodelling resulting in the progression of the disease. On the other hand, high cytosolic levels of stefins may be relevant for regulation of apoptosis, when initiated via lysosomal cell death pathway inhibiting cathepsin B, which was proposed as a dominant execution protease in the lysosomal apoptotic pathways, induced in a variety of tumour cells by tumour necrosis factor alpha (TNF-alpha). In some studies lower levels of stefins in tumours have been reported. Lower mRNA levels of stefin B have been reported in breast and esophagus tumours as compared to adjacent control tissues.

Although stefins are cytosolic proteins, they have also been detected in body fluids of cancer patients. Stefin B has been detected in ascitic fluid from patients with ovarian carcinoma and in bronhoalveolar fluid of lung cancer patients.

Diagnosis: The poor survival rate of hepatocellular carcinoma is in part due to the inability to diagnose patients at an early stage. Stefin B is specifically overexpressed in most hepatocellular carcinoma and is also elevated in the serum of a large proportion of hepatocellular carcinoma patients. Stefin B may be a useful marker for diagnosing patients with hepatocellular carcinoma with a high sensitivity.

Prognosis

Higher levels of stefin B in tumour tissues have been shown to correlate with a favourable prognosis of cancer patients. A significant prognostic value of stefin B was determined in patients with lung and head and neck cancer. On the other hand, animal model with excluded expression of stefin B did not support its suppressive function in cancer. A significantly lower metastatic spread was detected in stefin B knock-out mice than in wild-type animals. Similarly, higher levels of stefin B in body fluids have been associated with a poor prognosis of cancer patients. Alterations in secretion may result in higher extracellular and lower intracellular levels of stefins and, therefore, a reverse correlation with patient' survival is to be expected.

Oncogenesis

Increased levels of cysteine protease activity, not being balanced by a corresponding increase of cysteine protease inhibitors are associated with progression of malignant disease and poor patient's prognosis. Enhanced expression of stefin B would be expected to diminish the tumour-associated proteolytic activity and indeed, there is evidence of a suppressive role of stefin B in various cancer types.

Progressive myoclonus epilepsy

Disease

The progressive myoclonus epilepsy of the Unverricht-Lundborg type (EPM1) is an autosomal recessive disease characterized by progressive myoclonic jerks and decline in cognition. Genetic linkage studies, suggest the involvement of the stefin B gene. A decreased amount of stefin B mRNA is a common finding in EPM1 patients and it may be due to: 1) a mutation in the promoter region causing a decrease in the rate of transcription of the gene or 2) mutations of the coding region/splice sites that may inhibit translation or diminish the half-life of the transcript and/or of the protein. The availability of a stefin B knock-out mouse as a model for the disease has allowed identification of the presence of severe apoptotic damage to the cerebellar granule cells. This observation combined with the anti-protease function of stefin B protein has suggested that it
may have an anti-apoptotic function in the cerebellum. It was shown that a number of proteins (manly proteins that are involved in the regulation of cytoskeletal functions) that are not proteases can interact specifically with stefin B, forming a multiprotein

complex. The first hypothesis is that stefin B may be active as antiprotease, protecting the complex against the attack of proteases. An alternative hypothesis is that stefin B may bind to the interacting proteins modifying the structure, thus allowing the correct formation of the complex. A further hypothesis is the sequestration of stefin B by the multiprotein complex, thus impeding its interaction with cathepsins.

References

Ritonja A, Machleidt W, Barrett AJ. Amino acid sequence of the intracellular cysteine proteinase inhibitor cystatin B from human liver. Biochem Biophys Res Commun. 1985 Sep 30;131(3):1187-92

Pennacchio LA, Myers RM. Isolation and characterization of the mouse cystatin B gene. Genome Res. 1996 Nov;6(11):1103-9

Brown WM, Dziegielewska KM. Friends and relations of the cystatin superfamily--new members and their evolution. Protein Sci. 1997 Jan;6(1):5-12

Kos J, Lah TT. Cysteine proteinases and their endogenous inhibitors: target proteins for prognosis, diagnosis and therapy in cancer (review).

Oncol Rep. 1998 Nov-Dec;5(6):1349-61

Kos J, Krasovec M, Cimerman N, Nielsen HJ, Christensen IJ, Brünner N. Cysteine proteinase inhibitors stefin A, stefin B, and cystatin C in sera from patients with colorectal cancer: relation to prognosis. Clin Cancer Res. 2000 Feb;6(2):505-11

Turk V, Kos J, Turk B. Cysteine cathepsins (proteases)--on the main stage of cancer? Cancer Cell. 2004 May;5(5):409-10

Keppler D. Towards novel anti-cancer strategies based on cystatin function. Cancer Lett. 2006 Apr 28;235(2):159-76

Joensuu T, Kuronen M, Alakurtti K, Tegelberg S, Hakala P, Aalto A, Huopaniemi L, Aula N, Michellucci R, Eriksson K, Lehesjoki AE. Cystatin B: mutation detection, alternative splicing and expression in progressive myclonus epilepsy of Unverricht-Lundborg type (EPM1) patients. Eur J Hum Genet. 2007 Feb;15(2):185-93

Cipollini E, Riccio M, Di Giaimo R, Dal Piaz F, Pulice G, Catania S, Caldarelli I, Dembic M, Santi S, Melli M. Cystatin B and its EPM1 mutants are polymeric and aggregate prone in vivo. Biochim Biophys Acta. 2008 Feb;1783(2):312-22

Lee MJ, Yu GR, Park SH, Cho BH, Ahn JS, Park HJ, Song EY, Kim DG. Identification of cystatin B as a potential serum marker in hepatocellular carcinoma. Clin Cancer Res. 2008 Feb 15;14(4):1080-9

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