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Gene Section
Mini Review

CSTA (cystatin A (stefin A))

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Identity

Other names: Cystatin-A; Cystatin-AS; STF1; STFA; Stefin-A

HGNC (Hugo): CSTA

Location: 3q21.1

DNA/RNA

Description

The gene for human stefin A is located on chromosome 3q21 and it comprises three exons of 111 bp, 102 bp and 226 bp in length, while the lengths of the 1st and 2nd intron are approximately 14 Kbp and 4 Kbp, respectively. The conserved sequence of QVVAG is encoded in the 2nd exon and is not inserted by any introns.

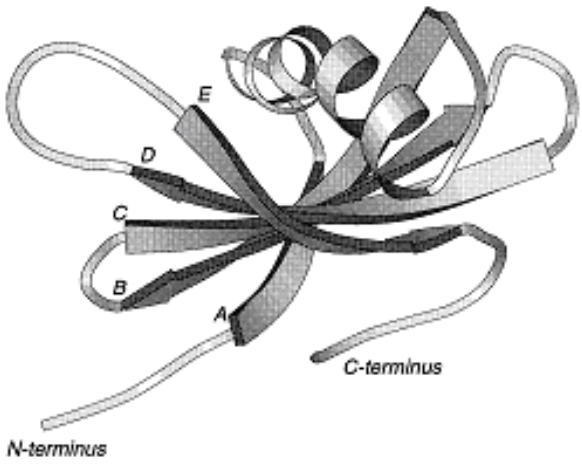
Transcription

The transcript length of stefin A mRNA is 294 bps. Binding sites for AP-2 (Activating Protein 2) and Sp1 (Selective Promoter Factor 1) regulatory elements are present in the promoter region and an AP-1 (Activating Protein 1) binding site in the 1st intron.

Protein

Description

Stefin A belongs to the cystatin superfamily of cysteine protease inhibitors. The lack of a signal sequence and disulfide bonds makes stefins distinct from other members of the cystatin superfamily.
Human stefin A is a single chain protein consisting of 98 amino acid residues, with a molecular mass of 11 kDa. Stefin A is an acidic protein with pI values between 4.5 - 5.0. Like other members of the cystatin superfamily, stefin A 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 10-8M) .



Ribbon representation of the minimised average structure of stefin A, illustrating the 5-stranded antiparallel b-sheet (with the strands marked A to E) wrapped around the central a-helix with the C-terminal loop running along the convex face of the sheet (Martin et al., 1995).

Expression

Stefin A is expressed and localized most abundantly in epithelial and lymphoid tissue.

Function

Besides protection of cytosolyc and cytoskeleton proteins from degradation by cysteine proteases accidentally released from lysosmes, several other functions have been suggested for stefin A. It may be important in the control of normal keratinocyte proliferation and differentiation. Also, it has been proposed to play a role in apoptosis, since apoptotic

bodies consistently stain for inhibitor, which also correlates with p53 activation. Stefin A should also protect epithelial and lymphoid tissues from cysteine proteases produced by pathogens invading the body. Increased levels of stefin A were found in inflammatory skin samples and psoriatic epidermis and in inflamed gingival tissue homogenates from patients with periodontal inflammatory diseases. Recent genetic studies identified also mouse stefin A to be involved in a control of ovarian follicular growth and maturation.

Homology

Human stefin A exhibit a high degree of homology to other cysteine protease inhibitors of the cystatin superfamily which includes human stefin B and the homologues in other species such as cystatins alpha and beta in rat, bovine thymus stefin C, porcine thymus stefins D1 and D2, mouse stefins A(1-4) and others.

Implicated in

Invasive cancers

Disease

Higher levels of stefin A in tumours have been determined in lung cancer, breast cancer, head and neck cancer 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 stefin A 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. For example, stefin A immunoreactivity was lower in lymphomas, in tumours of squamous epithelial cell origin as well as in prostate and brain tumours. Lower mRNA levels of stefin A have been reported in breast and esophagus tumours as compared to adjacent control tissues.

Although stefins are cytosolic proteins, stefin A has also been detected in body fluids of cancer patients, such as ascitic fluid from patients with ovarian carcinoma and in bronhoalveolar fluid of lung cancer patients. Increased serum levels of stefin A in patients with hepatocellular carcinoma and liver cirrhosis correlated with tumour size and with a number of neoplastic lesions. Stefin A were moderately increased also in patients with colorectal cancer or lung cancer.

Prognosis

Higher levels of stefin A in tumour tissues have been shown to correlate with a favourable prognosis of cancer patients. A significant prognostic value of stefin A was determined in patients with lung and head and neck cancer. In the latter, high stefin A tumour levels were found as a strong factor for prediction of prognosis also in multivariant analysis when correlated with established clinical parameters. In prostate tumours higher cathepsin B/stefin A ratio were associated with more aggressive behaviour of prostate cancer. On the other hand, higher levels of stefin A 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 stefin A, 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 A would be expected to diminish the tumour-associated proteolytic activity and indeed, there is evidence of a suppressive role of stefin A in various cancer types. Transfection of stefin A cDNA into human EC9706 esophageal squamous cell carcinoma cells inhibits tumour growth, angiogenesis, invasion, and metastasis, and this is mainly through the inhibiting of cathepsin B activity.

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