Gene Section
Review

CTSH (cathepsin H)

Zala Jevnikar, Janko Kos

Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

Identity

Hugo: CTSH
Other names: ACC-4; ACC-5; CPSB; DKFZp686B24257; EC 3.4.22.16; MGC1519; aleurain; minichain
Location: 15q25.1

DNA/RNA

Description

The gene for human cathepsin H is located on chromosome 15q24-q25 and contains 12 exons spanning over 23 kb of genomic sequences. The junctions between the exons and 11 introns conform to the GT-AG rule. The preproenzyme transcript length is 1005 bp.

Transcription

The cathepsin H gene has a TATA- and CAAT-less promoter and upstream of exon 1 only one GC box was detected, suggesting the presence of one more exon. Two different forms of cathepsin H cDNA, the full-length form (CTSH) and a truncated form with deletion of 12 amino acids at the signal peptide region (CTSHdelta10-21), were identified in prostate tissues and cancer cell lines.

Protein

Description

Cathepsin H belongs to the superfamily of papain-like cysteine proteases. It is synthesized as a preproenzyme of 335 amino acid residues with a calculated Mr of 37 403. It is proteolytically processed to an active single chain, i.e. mature form within the endosomes/lysosomes. A unique feature of this enzyme is that it acts as both an aminopeptidase and an endopeptidase although the latter activity is much lower than the former activity. Sequencing data revealed that in addition to the heavy and light chains, which are typically found in a number of mammalian papain-like cysteine proteases, cathepsin H contains also an octapeptide EPQNCSAT originating from the propeptide, termed the mini-chain. It was shown that the mini-chain is disulfide linked to Cys205 of the main body of the enzyme and involved in the aminopeptidase activity of the enzyme. It was concluded that the mini-chain plays a key role in substrate recognition, and that the carbohydrate residues attached to the body of the enzyme are involved in the positioning the mini-chain in the active-site cleft. Procathepsin H has three potential carbohydrate binding sites. Glycosilation has been confirmed on Asn230 and on the mini-chain Asn101 of the mature enzyme. The recombinant form of human cathepsin H lacking the mini-chain was shown to be an endopeptidase. Cathepsin H hidrolyzes endopeptidase substrates such as Bz-Arg+NHNap, Bz-Arg+NHMec, Bz-Phe-Val-Arg+NHMec, and acts on Pro-Gly+Phe and Pro-Arg+NHNap much like a dipeptidyl-peptidase. It was shown to cleave several proteins preferring hydrophobic residues at P2 and P3, however the endopeptidase activity of the enzyme is limited. Collagen and laminin, for instance, were not degraded by cathepsin H. Naturally occurring inhibitors of cathepsin H are the cystatins, a2-macroglobulin and antigens from mouse cytotoxic lymphocytes CTLA-2β.

Expression

Cathepsin H expression is ubiquitous, with very high expression in the kidney. There is growing evidence that the expression of cathepsin H is increased in diseases including breast, colorectal and prostate carcinoma, melanoma and gliomas. In contrast, decreased cathepsin H expression has been reported in squamous cell carcinoma of the head and neck. Other studies have found a higher cathepsin H expression in well-differentiated pancreatic cancer cells compared with less well-differentiated cancer cells.
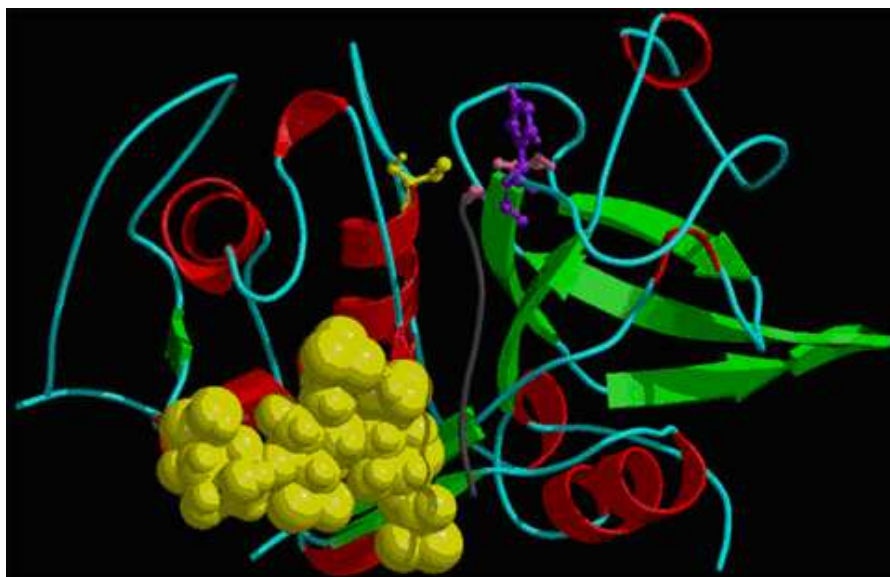
Richardson diagram of cathepsin H structure: a-helixes are shown in red and β -sheets in green. Catalytic residues are shown in ball-and-stick representation: Cys141 in yellow, His281 in purple and Asn301 in pink. Carbohydrates are shown as CPK spheres in yellow. The mini chain is shown in grey (MEROPS: the peptidase database - C01.040).

Localisation

Cathepsin H is located manly at the endosomal-lysosomal compartments. Only 10% of the enzyme is secreted. It has been shown that substantial concentrations of cathepsin H circulate in the blood.

Function

Cathepsin H is one of the lysosomal cysteine proteinases, which are involved in intracellular protein degradation. It is one of the few noncomplement proteases that cleave native C5 to generate the potent chemotaxin C5a. Cathepsin H was detected in extracellular compartments of atherosclerotic plaques. Although the pathogenic potential of cathepsin H in the development of the late, unstable plaque is quite evident, there is the possibility that this protease may play a role in early atherogenesis. Furthermore, it was found that cathepsin H could contribute to the transformation of LDL in monocyte-derived foam cells. Recently the enzyme was shown to be essential in one of the processing steps of hydrophobic surfactant-associated protein C.

Cathepsin H is overexpressed in different tumour cells. However, the role of cathepsin H in tumour progression is not well understood. A possible function of cathepsin H in tumour progression is its ability to degrade fibrinogen and fibronectin, suggesting that, along with other proteases, cathepsin H may be involved in the destruction of extracellular matrix components leading to cancer proliferation, migration, and metastasis.

Homology

Cathepsins H exhibit a high degree of sequence homology to cathepsin B and other cysteine proteinases of the C1 (papain) family.

Mutations

Germinal

Not yet reported

Somatic

Not yet reported

Implicated in

Colorectal cancer

Prognosis

Protein levels of cathepsin H were measured by ELISA in preoperative sera from 324 patients with colorectal cancer. The level of cathepsin H was significantly increased in patient sera, the median level was 8.4 ng/mL versus 2.1 ng/mL in 90 healthy blood donors (p < 0.0001). In survival analysis a significant difference was found between the group of patients with low cathepsin H (first tertile) who had a poor prognosis and the remaining patients (p = 0.03). The risk of patients was further stratified when cathepsin H levels were combined with carcinoembryonic antigen (CEA). Patients with high CEA and low cathepsin H had the highest risk of death with a hazard ratio of 2.72 (95% CI 1.73-4.28), p < 0.0001.The prognostic information of cathepsin H differs from that of the related cathepsins B and L and suggest different roles during the progression of malignant disease.

Melanoma

Prognosis

The level of cathepsin H was determined in the sera of 43 patients with metastatic melanoma, in 54 patients

with treated cutaneous melanoma with no evidence of metastatic disease, and in 30 healthy blood donors, using quantitative ELISA. The levels were significantly higher within the group of metastatic melanoma patients compared with the healthy controls with a median of 13.7 versus 4.9 ng/ml (P < 0.0001). Cathepsin H was also significantly increased within the group of melanoma patients with no metastasis, with a median of 9.6 ng/ml. The serum level was increased in patients showing no response to the chemoimmunotherapy as compared to the level in responders. Metastatic melanoma patients with high content of cathepsin H experienced significantly shorter overall survival rates than the patients with low levels of the enzyme (Cat H: P < 0.006 and relative risk, 2.4, using median as cut-off value).

Head and neck carcinoma

Prognosis

To estimate the prognostic value of cathepsins H in head and neck carcinoma, its concentration was measured in cytosols of primary tumours and adjacent normal tissue from 21 patients. Cathepsin H concentration was higher in normal tissue (p = 0.001) than in tumour tissue and in laryngeal than in non-laryngeal normal and tumour tissues. Disease-free survival was poor in patients with lower concentrations of cathepsin H in tumour tissue (p = 0.055).

Bladder cell transitional cell carcinoma

Note: Using spectrofluorometric assay, catalytic activity of cathepsin H was measured in human bladder cell lines (HCV29, normal; RT4, well differentiated; J82, poorly differentiated) and in noncancerous and cancerous tissue samples (n = 20) of transitional cell carcinoma. In comparison to the intracellular activity of cathepsin H in the poorly differentiated cell line J82, the intracellular activity in the normal cell line HCV29 was significantly greater (P <0.05), independent of stage or grade. In contrast, the portion of cathepsin H released from cell line J82 into the supernatant, revealed higher values than that from cell line HCV29. In cancerous bladder tissue, the level of cathepsin H was significantly greater than in the matched normal tissue (P <0.05).

Lung cancer

Note: A transgenic mouse model of lung cancer was utilized to identify markers of early lung tumours in humans. Immunohistochemical analyses identified cathepsin H as being consistently elevated in the murine lung tumours compared to non-tumour bearing transgenic lung tissue surrounding the tumour. Importantly, the elevation was observed in early stage, indicating its ability to detect early lung lesions that would be amenable to surgical resection.

Glioma

Note: Cathepsin H activity was determined in normal brain tissue and tumour tissue extracts. The activity of cathepsin H was twofold higher in low grade glioma, fourfold higher in anaplastic astrocytoma and eightfold higher in glioblastoma than in normal brain tissue. Cathepsin H antibody inhibited the invasion of glioblastoma cell lines through Matrigel®. These data suggest that the tumour-specific increase in antigen may be a useful independent marker of tumour progression in central nervous system neoplasms.

Cervical carcinoma

Note: The expression of cathepsin H in cervical carcinoma cell lines and tissue was found to be down-regulated compared to normal tissue, using cDNA arrays.

Joint diseases

Note: The level of cathepsin H was determined in synovial fluids and sera of patients with inflammatory and metabolic joint diseases, using quantitative ELISA. Cathepsin H was not found in normal sera (values below 3 micrograms/l), but was measurable in patients' synovial fluids. The highest values of cathepsin H were measured in synovial fluids of patients with undifferentiated arthritis. There is yet no clear correlation between the quantity of the enzyme released in synovia and the clinical diagnosis or the stage of disease.

Alzheimer's disease

Note: Cultured fibroblasts from patients affected by Alzheimer's disease (AD) exhibited alterations of the enzyme transketolase. Abnormalities (dubbed alkaline band) consisted of enzyme forms having unusually high pI and were proposed as a marker of the disease in living patients. Human cathepsin H was shown to partially induce an Alzheimer-like transketolase pattern and cleave normal transketolase to a 35 kDa fragment as spontaneously occurring in Alzheimer's disease fibroblasts. The explanation of transketolase abnormalities could be an imbalance of proteolysis in Alzheimer's disease fibroblasts due to a relative increase/derangement of cysteine proteinases, including cathepsin H.

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