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REVIEW

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Cathepsin E (EC 3.4.23.34) — a review

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Abstract: Cathepsin E belongs to the third class of enzymes — hydrolases, a subclass of peptide bond hydrolases and a sub-subclass of endopeptidases with aspartic catalytic sites. Cathepsin E is an endopeptidase with substrate specificity similar to that of cathepsin D. In a human organism, cathepsin E occurs in: erythrocytes, thymus, dendritic cells, epithelial M cells, microglia cells, Langerhans cells, lymphocytes, epithelium of gastrointestinal tract, urinary bladder, lungs, osteoclasts, spleen and lymphatic nodes. In human cells, loci of the gene of pre-procathepsin E are located on chromosome 1 in the region 1231-32. The catalytic site of cathepsin E is two residues of aspartic acid — Asp96 and Asn281, occurring in amino acid triads with sequences DTG96-98 and DTG281-283. To date, no particular role of cathepsin E in the metabolism of proteins in normal tissues has been found. However, it is known that there are many documented pathological conditions in which overexpression of cathepsin E occurs. (*Folia Histochemica et Cytobiologica 2011; Vol. 49, No. 4, pp. 547–557*)

Key words: cathepsin E, cathepsin D

Introduction

Cathepsin E was first described in 1962 by Lapresle and Webb [1]. It belongs to the third class of enzymes — hydrolases, a subclass of peptide bond hydrolases and a sub-subclass of endopeptidases with aspartic catalytic sites. Cathepsin D, pepsin and renin belong to the same sub-subclass [2]. Initially, cathepsin E was described as a pepsin-like endopeptidase [3], a slow-moving proteinase [4] or erythrocyte membrane acid proteinase [5]. Later, it was proved immunochemically and biochemically, and confirmed thanks to the determination of the identical structure of the above-mentioned endopeptidases, that all of them are the same enzyme — cathepsin E [4–7]. Cathepsin E is similar to cathepsin D. It differs from the latter, however, in that it has a broader substrate specificity, a lower optimum pH (2.5–2.8), it occurs in different cell organelles and occurs only in some kinds of cells and tissues [2]. The differences between cathepsin E and cathepsin D are summarized in Table 1.

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Distribution

In human and animal organisms, cathepsin E occurs only in some cells, tissues and organs, and the cells, tissues and organs differ depending on the particular animal species [8]. In a human organism, cathepsin E occurs in: erythrocytes, thymus, dendritic cells, epithelial M cells, microglia cells, Langerhans cells, lymphocytes, epithelium of gastrointestinal tract, urinary bladder, lungs, osteoclasts, spleen and lymphatic nodes [9–14]. However, it does not occur in human neutrophiles or bovine erythrocytes [15] (Table 2). The content of cathepsin E in various rat tissues is presented in Table 3. The intracellular transport and distribution of cathepsin E are also very distinctive. Unlike pepsin and renin, this peptidase is not secreted to the lumen of the digestive tract, and is not directed to lysosomes like cathepsin D. Its characteristic place of occurrence is endoplasmic reticulum and Golgi apparatus [10, 16]. Only in erythrocytes does it occur on the cytoplasmic surface of cell membrane [17].

The gene encoding cathepsin E

In human cells, loci of the gene of pre-procathepsin E are located on chromosome 1 in the region 1231-32 [18]. The gene of cathepsin E comprises nine exons.

Table 1. Differences between cathepsin E and cathepsin D

Distinctive feature	Cathepsin E	Cathepsin D
Encoding gene	Chromosome 1, region 1q31-32	Chromosome 11, region 11p15.5
Molecular weight (mature form)	82	46
Optimum pH in acting toward hemoglobin	2.0 (temp. 45°C)	3.5 (temp. 37°C)
Phosphorylation of mannose residues to mannose-6-phosphate	No occurrence	Occurrence
Molecular location	Plasma membranes, endoplasmic reticulum	Lysosomes
Activity inhibited by inhibitor from human ascaris	Inhibition	No inhibition
Protein substrate	Human albumin	Bovine globin
Specific polypeptide substrate	Substance P	β-endorphin
Antigenic characteristics	Various	Various

Table 2. Distribution of cathepsin E in mammalian blood cells, as revealed by a combined application of elctrophoretic and immunochemical methods

	PMN*	MNL**	Erythrocyte ghost
Human	–	–	+
Rat	+	+	+
Guinea pig	+	+	–
Pig	–	–	–
Cow	–	–	–
Goat	–	–	–

*Polymorphonuclear leukocytes; **Mononuclear leukocytes

It encodes the signal peptide, propeptide and the active part of cathepsin E. Expression of the encoding gene and occurrence of cathepsin E is limited to specific cells [19]. In some human cells, splicing variants of mRNA, participating in cathepsin E synthesis, have been discovered [20–23]. Splicing results in the removal of exon 7, which encodes the Asp40 residue in the fragment -Asp40-Thr41-Gly42- of the second active center [23]. The monomeric, unstable form of cathepsin E occurs in gastric carcinoma cells [24]. By means of recombination, a mutated form of cathepsin E has been obtained, in which the unique Cys4 residue is substituted with Ala or Ser residue [25]. Mutated cathepsin E is less stable than natural cathepsin E, but its activity and sensitivity to inhibitors remains unchanged.

Biosynthesis

Cathepsin E is synthesized as a pre-proenzyme made up of 438 amino acid residues. Cleavage of an 18-amino acid propeptide results in the creation of procathe-

Table 3. Levels of cathepsin E in various rat tissues

Sources	Cathepsin E [μg/mg of protein]
Brain tissues	
Cerebral cortex	0.0004*
Cerebellum	0.0037*
Hippocampus	0.0017*
Neostriatum	0.0005*
Gastrointestinal tracts	
Stomach	1.05 (1.130*)
Jejunum	0.03
Colon	0.10
Esophagus	ND
Liver	ND
Lymphoid tissues	
Cervical lymph node	0.18
Thymus	0.19
Spleen	0.18
Bone marrow	0.13
Urinary organs	
Urinary bladder	0.19
Kidney	0.005
Secretory tissues	
Submandibular gland	0.006
Lacrymal gland	ND
Adrenal	ND
Blood cells	
Erythrocytes	0.002
Lymphocytes	0.09
Platelets	0.004
Peritoneal neutrophiles	0.10
Organs	
Lung	0.03 (0.04*)
Heart	ND (0.0012*)
Skeletal muscle	ND
Skin	0.03

*Values from ELISA; ND — not detectable

Table 4. Amino acid composition of signal peptide, propeptide, procathepsin E and cathepsin E of a human

Amino acid	Signal peptide	Propeptide	Procathepsin E	Cathepsin E
Ala A	1	2	21	19
Arg R	0	5	9	4
Asn N	0	1	13	12
Asp D	0	1	21	20
Cys C	0	0	7	7
Gln Q	1	3	23	20
Glu E	1	1	14	13
Gly G	0	1	40	39
His H	0	3	8	5
Ile I	0	1	20	19
Leu L	10	6	29	23
Lys K	1	4	9	5
Met M	1	1	10	9
Phe F	0	2	21	19
Pro P	0	2	25	23
Ser S	0	5	40	35
Thr T	1	0	22	22
Trp W	0	1	5	4
Tyr Y	0	0	13	13
Val V	2	1	30	29
Number of amino acid residues	18	40	420	380
Molecular weight (Da)	2,307	5,344	47,560	42,215

psin E. The molecular weight of procathepsin E is 90,000 Da. It is a homodimer containing an intramolecular -S-S- bridge. In acidic pH, auto-activation of procathepsin E, cleavage of a 40-amino acid propeptide and creation of the mature form of cathepsin E occurs, as presented in Table 4 and Figure 1 [26].

The propeptide has a strong positive charge, as it contains five residues of alkaline amino acids and only two residues of acidic amino acids. Hence a hypothesis arises that the propeptide binds to the active form mostly by electrostatic effect. Thanks to that, procathepsin E is prone to auto-activation after a short time in acidic pH, as a result of which it is transformed into the mature form. The mature form is made up of 380 amino acid residues and its molecular weight is 42 kDa [27], (Figure 2). The catalytic site is made up of Asp98, Asp283 and Thr284 (DTG) residues [27] (Figure 3). The -S-S- bridge between two residues Cys34 in the N-terminus of the molecule results in a homodimer appearing. The -S-S- bridge is responsible for the stability of that peptidase in neutral pH. Thanks to that, the active site is made up of two homologous domains, containing sequences of tripeptide DTG [2]. The two domains comprise the active site. The DTG sequence occurs in cathepsin E molecules in humans and all animal species except rabbit cathepsin E [28].

Figure 1. Alignment of the deduced amino acid sequences of procathepsin E from human. The sequence for the murine procathepsin E is given in full. At any given position where no residue is shown, sequence identity with murine procathepsin E exists. The positions of the active sites aspartic acid residues, potential N-linked glycosylation sites and the Cys residue involved in the formation of the interchain disulfide bridge are indicated by ▼, ◇ and □ respectively

A molecule of cathepsin E is N-glycosylated by connecting high-mannose oligosaccharides or com-

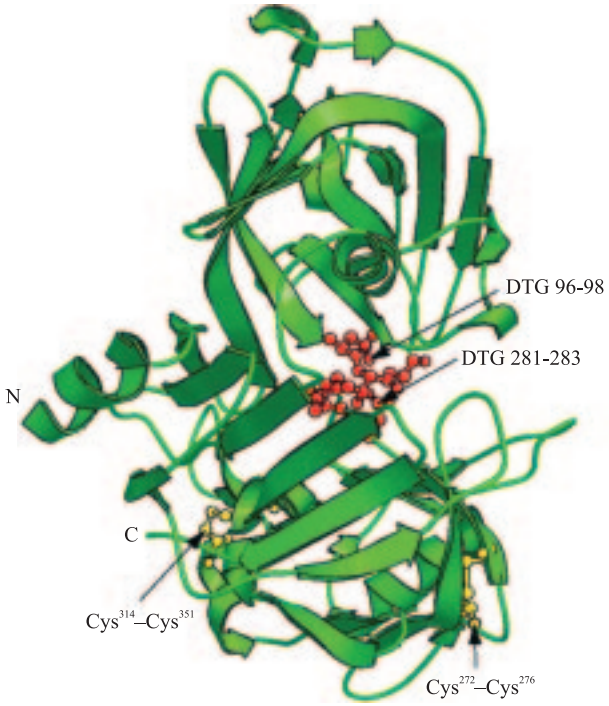


Figure 2. The computed structure of cathepsin E. The main chain is shown by ribbon drawing. The residues at the DTG/DTG active site and those involved in forming disulfide bonds are shown with ball-and-stick drawing; the former is colored red and the latter yellow

plex oligosaccharides [29]. The sites of glycosylation are Asn residues. Cathepsin E of gastric mucosa contains high-mannose oligosaccharides, while cathepsin E of human erythrocytes contains complex oligosaccharides [10, 30, 31].

Neither activation of procathepsin E nor its sensitivity to inhibitors is dependent on the presence or type of oligosaccharides. Glycosylation does not affect the stability of cathepsin E in low pH either. Still, the oligosaccharide component increases its stability in neutral pH and its immunity to higher temperature. ATP participates in stabilizing cathepsin E in pH 7.0 [32].

Purification

In order to obtain a highly purified preparation of cathepsin E, we first need to find a tissue including the greatest amounts possible of that peptidase. Differences in enzyme and protein composition of cells and tissues necessitate individual preparation solutions. In the preliminary phases of cathepsin E purification, methods commonly used for isolation and purification of proteins are applied, such as isoelectric point precipitation, ammonium sulphate and organic solvents fractionation, Sephadex gel molecular

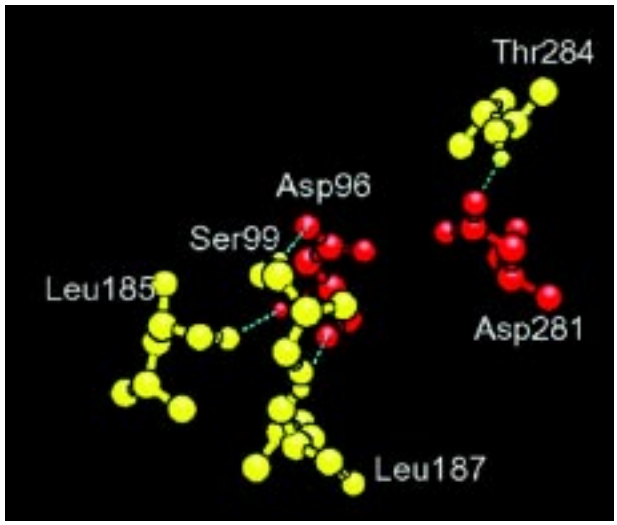


Figure 3. Place of activity of cathepsin E

filtration, ion-exchange chromatography on DEAE--cellulose, ConA sepharose or FPIC Mono Q column [2]. The final phases of purification are affinity chromatography on agarose bound to pepstatin or to an antibody against cathepsin E [2]. A homogenous preparation of mature cathepsin E has been obtained from human gastric mucus [4], human erythrocytes [33] and rat spleen [34], neutrophiles [35] and epidermis [36]. Cathepsin E preparations are kept at –20°C, in buffer with pH 7.0 containing 50% glycerol.

Obtaining a highly purified preparation of procathepsin E is difficult, as affinity chromatography cannot be used [37, 38]. Procathepsin E was obtained by means of recombination from bacteria *E. Coli* [39, 40]. Recombinant human cathepsin E has also been purified from ovaries of Campbell's dwarf hamster [41] and from *Pichia pastoris* [42]. Procathepsin E is auto-activated in acidic pH [2, 43].

Specificity of activity

Cathepsin E is an endopeptidase with substrate specificity similar to that of cathepsin D. It expresses high affinity to hydrophobic amino acid residues in P1 and P1' positions of substrates [44]. In P2 position, unlike cathepsin D, there may be a residue of lysine [45]. In P2' position, there is a broad structural spectrum of amino acid residues, including residues of polar amino acids [46]. In an oxidized B chain of bovine insulin, cathepsin E cleaves the peptide bond presented in Figure 4. Only the first of these bonds is not cleaved by cathepsin D. Cathepsin E cleaves six peptide bonds in the B chain of insulin. Specificity of cathepsin E has also been tested on proteins: tetanus toxin [47], glycoprotein and mellitin from bee venom [48–50].

Mechanism of activity

The catalytic site of cathepsin E is two residues of aspartic acid — Asp96 and Asn281, occurring in amino acid triads with sequences DTG96-98 and DTG281-283. Carboxyl groups of amino acid residues activate a water molecule and act as proton donors and acceptors. The Asp96 carboxyl group is dissociated and the Asp281 carboxyl group is not. The dissociated Asp96 carboxyl group activates a water molecule and enables the release of a proton from it. As for the non-dissociated Asp281 carboxyl group, it polarizes the carboxyl group of peptide bond, facilitates the creation of tetraedric intermediate and enables the cleavage of that compound (Figure 5). After binding the substrate, two simultaneous transition reactions occur. The first reaction is transition of the proton from a water molecule to the carboxyl anion Asp96 and from the carboxyl group Asp281 to oxygen of the carboxyl group of the substrate. That results in creating a tetraedric intermediate. In the other reaction, peptide bonds are moved from the intermediate to the carboxyl ion Asp96 and from the carboxyl group Asp281 to the nitrogen atom. It causes hydrolysis of the substrate's peptide bond, appearance of the first product of reaction with a free carboxyl group and the second product of reaction with a free amino group, as well as recreation of the initial structure of the catalytic site of cathepsin E. Since those reactions are conducted by dissociating carboxyl groups of the catalytic site, the speed of the processes depends greatly on the pH of the environment. Cathepsin E is active in acidic environments with pH from 2.5 to 5.5.

Inhibitors

Diaso-acetyl-norleucine methyl ester is a synthetic inhibitor of cathepsin E, and the reaction is catalyzed with Cu^{2+} ions [51]. The chemical formula of that inhibitor is presented in Figure 6. The compound also inhibits the activity of cathepsin D.

A group inhibitor of aspartic endopeptidases (cathepsin E, cathepsin D, pepsin and renin) is pepstatin A [52] and its derivatives: acetyl- and isovaleryl-pepstatin [44, 53, 54] (Figure 7) [17].

An inhibitor of cathepsin E with narrow specificity is a polypeptide inhibitor isolated from human ascaris [4, 7, 39, 55]. It does not inhibit cathepsin D activity; however, it inhibits pepsin activity. Its molecular weight is about 17,000 Da. It is synthesized as an inactive form. At the N-terminus of the molecule, there is an amino acid sequence composed of 20 amino acid residues, cleaved off at activation; that is a signal propeptide. The active inhibitor is made up of 149 amino acid residues. It includes five Cys residues in positions 13, 48, 59, 79 and 146; it has three disulphuric bridges: Cys13-Cys59, Cys48-Cys66 and Cys79--Cys146. It has also been obtained by means of genetic recombination [56, 57]. The amino acid composition of that inhibitor is presented in Table 5, and the amino acid sequence in Figure 8 [58].

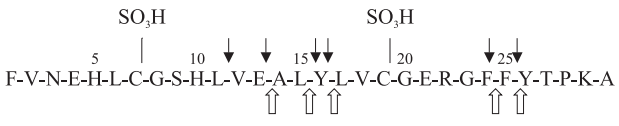


Figure 4. Peptide bonds cleaved in B chain of bovine insulin by cathepsin E and cathepsin D

↓ — place of activity of cathepsin E; ⇧ — place of activity of cathepsin D

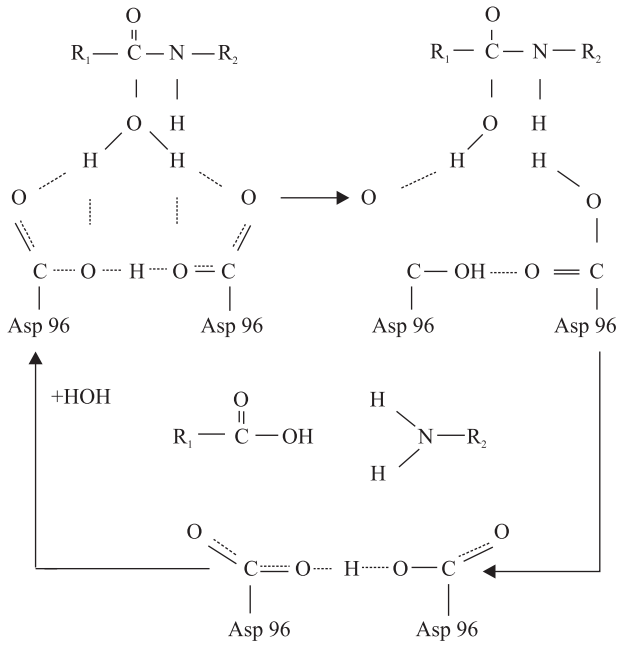


Figure 5. Diagram of peptide bond clevage by cathepsin E

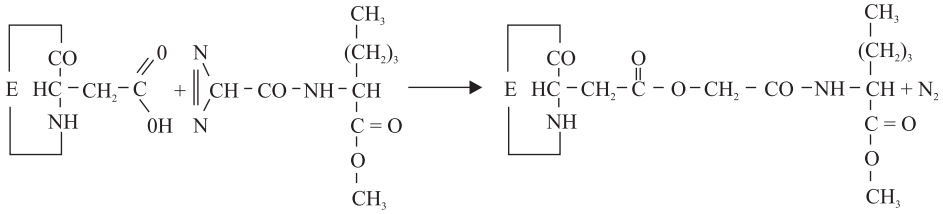
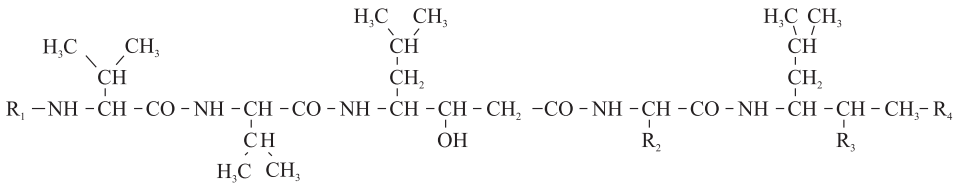


Figure 6. Reaction of cathepsin E with diaso-acetyl-D, L norleucine methyl ester



Pepstatins	R_1	R_2	R_3	R_4
A	iso-valeryl	$-CH_3$	–OH	–COOH
B	n-caproyl	$-CH_3$	–OH	–COOH
C	iso-caproyl	$-CH_3$	–OH	–COOH
D	n-heptanoyl	$-CH_3$	–OH	–COOH
E	iso-heptanoyl	$-CH_3$	–OH	–COOH
F	anteiso-heptanoyl	$-CH_3$	–OH	–COOH
G	n-capryl	$-CH_3$	–OH	–COOH
H	iso-capryl	$-CH_3$	–OH	–COOH
Hydroxypepstatine A*	iso-valeryl	$-CH_2-OH$	–OH	–COOH
Pepstanone A*	iso-valeryl	$-CH_3$	=O	–H

Figure 7. Structure of pepstatins, hydroxypepstatin and pepstanones. * — acyl radical R_1 — the same as pepstatins A–H

Table 5. Amino acid sequence of cathepsin E inhibitor from human ascaris

Amino acid	Signal peptide	Proinhibitor	Mature form
Ala A	2	17	15
Arg R	0	9	9
Asn N	0	7	7
Asp D	0	18	18
Cys C	0	16	16
Glu E	0	10	10
Gln Q	0	10	10
Gly G	0	6	6
His H	1	13	12
Ile I	2	8	6
Leu L	4	8	4
Lys K	0	7	7
Met M	1	2	1
Phe F	0	12	12
Pro P	0	3	3
Ser S	5	14	9
Thr T	1	4	3
Trp W	2	3	1
Tyr Y	1	1	0
Val V	1	1	0
Number of amino acid residues	20	169	149
Molelcular weight (Da)	18,658	2,262	16,396

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                10        20                30        50        40
QFLFSMSTGPFICTVKDNQVFVANLPWTMLEGDDIQVGKEFAARVEDCTNVKHDMA
    60        70                80        90        100       110
PTCTKPPPFCGPQDMKMFNFVGCSVLGNKLFIDQKYVRDLTAKDHAEVQTFREKIAA
    120               130       140       149
FEEQQENQPPSSGMPHGAVPAGGLSPPPPPDFCTVQ
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Figure 8. Amino acid sequence of cathepsin E inhibitor from human ascaris

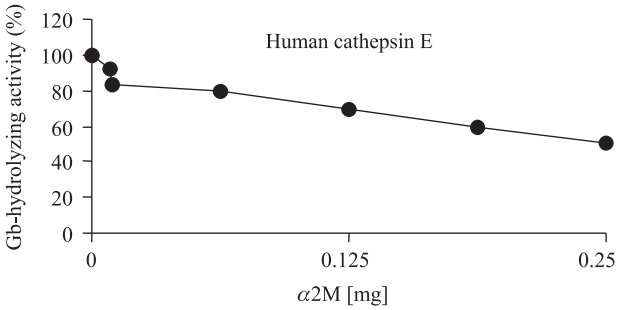

Figure 9. Effect of bovine α2M on the proteolytic avtivities of cathepsin E. The Gb-hydrolyzing activity of cathepsin E purified from human erythrocytes was measured at pH 3.8 in the absence or presence of increasing amounts of α2M

Table 6. Complexes of cathepsin E with a polypeptide inhibitor, α2-macroglobulin and a specific antibody

Inhibitor	Complex characteristics
Polypeptide inhibitor	Hydrophobic and ionic interaction of catalytic site with reactive site of the inhibitor, blocking of catalytic site
α2-macroglobulin	Limited proteolysis and conformation changes of α2-macroglobulin, creating a spatial block for macromolecular substrates
Antibodies against cathepsin E	Noncovalent bond of the antibody with cathepsin E, blocking of cathepsin catalytic site

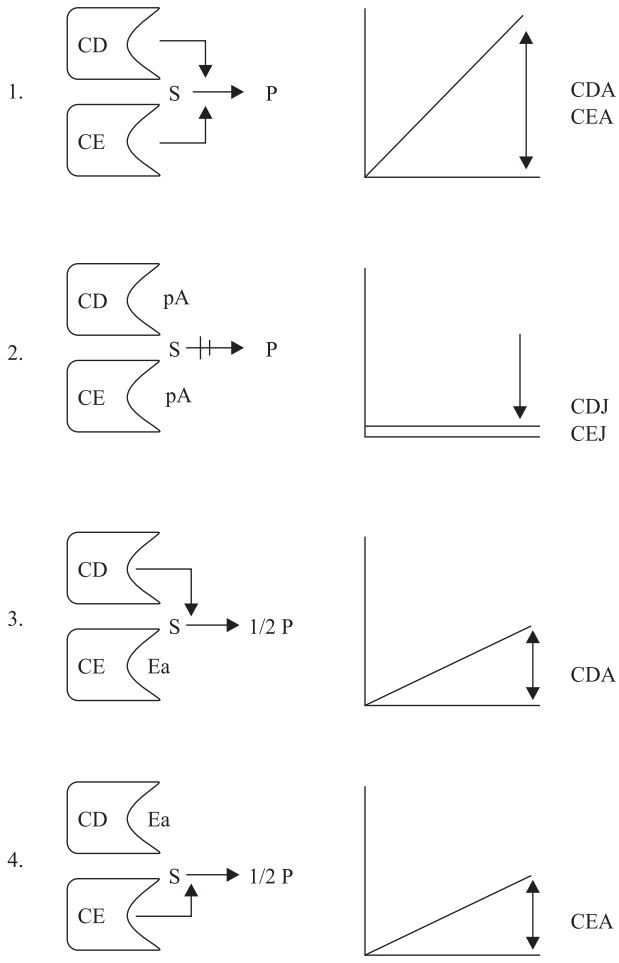

Figure 10. Principle of measurement of activity of cathepsin E (CE) and cathepsin D (CD) in equimolar mixture: 1 — total activity of CDA and CEA, 2 — inhibition of activity of both cathepsins by pepstatin A (pA), 3 — inhibition of cathepsin E by specific antibodies (CDA), 4 — inhibition of cathepsin D by specific antibodies (CEA). Based on a publication by Zaidi and Kalbachero [52]

Cathepsin E activity is also inhibited by a polyvalent endopeptidases inhibitor: alpha2-macroglobulin [59, 60] (Figure 9). Cathepsin E cleaves the -F811-L812-C peptide bond in the structure of that inhibitor.

A specific cathepsin E inhibitor is antibodies against that endopeptidase [52]. They allow for unambiguous differentiation between the activity of cathepsin E and cathepsin D found in a mixture (Table 6). It is illustrated in Figure 10, presenting inhibition of equimolar concentrations of those cathepsins found in the mixture.

Differences in sensitivity of cathepsin E, cathepsin D, pepsin and renin to inhibitors are presented in Table 7.

Determination of activity and concentration

Cathepsin E is an endopeptidase similar in specificity to cathepsin D. Both of them decompose, among others, blood serum albumin and globin. Yet, albumin is a substrate more specific for cathepsin E, and globin for cathepsin D [62–64] (Table 8).

Table 7. Vulnerability of human aspartyl proteases to inhibitors

Inhibitor*	Cathepsin E	Cathepsin D	Pepsin	Renin
Pepstatin A	+	+	+	+
Ascaris sp.derived inhibitor	+	–	+	–
Antibodies against cathepsin E	+	–	–	–
Antibodies against cathepsin D	–	+	–	–

* + inhibitory effect; – lack of inhibition

Table 8. Differences in proteins sensitivity to cathepsin E and cathepsin D activity with supplements

Protein	Cathepsin				
	E	D	E	D	E:D
	Optimum pH		Activity (%)		Ratio
Bovine globin	3.1	3.5	100	100	1.0
Human albumin	2.5	4.0	153	1	153.0
Bovine albumin	3.5	4.0	261	14	18.6
Bovine gamma-globulin	3.0	3.0	1	3	Approx. 0.3
Bovine casein	3.0	3.0	98	32	3.0

The optimum pH of cathepsin E in its activity towards albumin is pH 2.5, while in the case of cathepsin D, it is 3.5. Besides, cathepsin D is quickly deactivated in pH 2.5, especially at a temperature of 45°C. Peptides soluble in TCA, released from albumin by cathepsin E, are determined with a microbiuret reagent [61]. For determination of cathepsin E activity, a 10% solution of human blood albumin is used. Albumin (10 g) is dissolved in distilled water, brought to pH 2.5 with 1 mol/l HCl and complemented with water up to 100 ml; 0.5 ml of the tested material is added to 0.5 ml of albumin and incubated for 30 minutes at 45°C. The reaction is stopped by adding 1 ml of 4% trichloroacetic acid, following which the sample is incubated for 10 minutes at 45°C and centrifuged. 1.5 ml of biuret reagent is added to 1 ml of supernatant (1.5 g $CuSO_4 \times 5\ H_2O$ and 6.0 potassium sodium tartrate is dissolved in 500 ml of distilled water, 300 ml of 10% NaOH is added, and the volume is complemented to 1,000 ml with distilled water); after 30 minutes, extinction is read at 555 nm. The control test is carried out by adding the substrate and the enzyme to trichloroacetic acid. The results are read from the calibration graph made using human blood serum.

Globin is also a frequently used substrate; it is used for making zymograms as well [7]. The optimum activity of cathepsin E towards globin occurs in pH 3.0, and cathepsin D — in pH 3.5.

Certain polypeptides, such as beta-endorphin and neurokinine A are much better substrates for cathepsin E than proteins [14, 65]. Differences in the sensitivity of beta-endorphin and substance P to the activities of cathepsin E and cathepsin D are illustrated in Figure 11 [58].

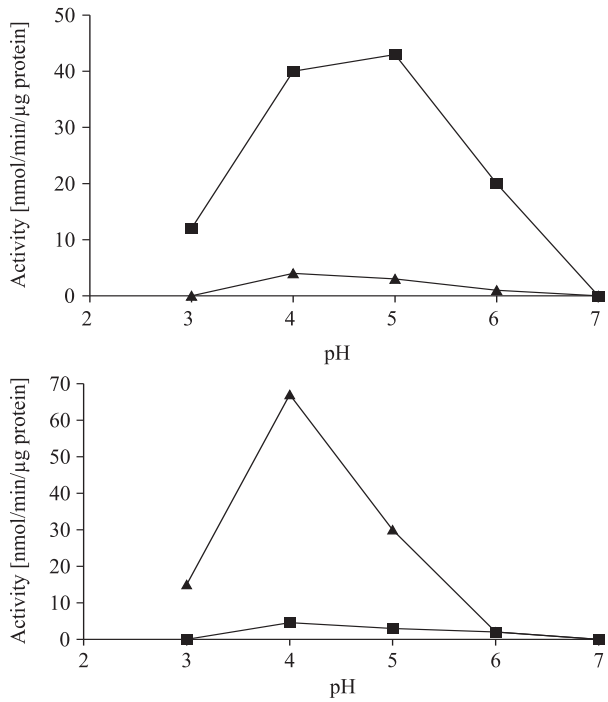

Figure 11. Hydrolysis of substance P (**A**) and β-endorophine (**B**) by cathepsin E (■) and cathepsin D (▲)

Synthetic peptide chromogenic and fluorogenic substrates [29] are based on the sequence of cleavage sites

Table 9. Hydrolytic activities of cathepsin E for bilogically active peptides in pH 5.0

Peptide	Activity [nmol/min/μg protein]
	Cathepsin E
Brain — gastrointestinal peptides	
Substance P	45.0
Neurokinin A	22.5
Eledoisin	11.5
Kassinin	3.2
Cholecystokinin — octapeptide	0.0009
Neuromedin C	UC*
Bombesin	UC*
Neurotensin	UC*
Growth-factor fragments	
Acidie FGF 102-111	2.7
Basic FGF 106-120	1.5
Opioid peptides	
β-endorphin	1.8
Dynorphin A	0.065
Vasoconstrictor peptides	
Porcine renin substrate	15.3
Human renin substrate	0.63
Big endothelin-1	0.11

* UC — uncleaved

in alpha2-Mg. The substrate Mca-Gly-Lys-Pro-Ile-Leu--Phe-Phe-Arg-Leu-Lys/Dnp/-D-Arg-NH_2 is hydrolyzed both by cathepsin E and by cathepsin D. Cathepsin D is removed from the samples by means of immunoprecipitation with the use of specific antibodies. The remaining activity is cathepsin E. Synthetic peptide substrates Lys-Pro-Ile-Glu-Phe+Nph-Arg-Leu and Pro-Pro-Thr--Ile-Phe+Nph-Arg-Leu contain a p-nitrophenylalanine residue in position P1', where it serves the function of a chromogenic indicator group [66]. That allows for spectrophotometric determination, but there are some limitations: change of absorbance is only detected in pH over 6.0 and must be measured at the wavelength of 300 nm [66]. The measurements are carried out in pH 3.0–3.5. The chromogenic peptide Mca-Gly-Lys-Pro-Ile-Leu--Phe+Plo-Arg-Leu-Lys/Dnp/-NH2 is cleaved by cathepsin E and cathepsin D but the former is active in pH 2.0 and the latter is not active in such pH [29].

Concentration of cathepsin E is determined with the use of specific antibodies, by means of titration of the catalytic site with pepstatine and with the use of a calibration graph presenting the dependence of activity on the concentration of highly purified cathepsin E preparation [38].

The role of cathepsin E in pathobiochemistry

So far, no particular role of cathepsin E in the metabolism of proteins in normal tissues has been found. However, it is known that there are many documented pathological conditions in which overexpression of cathepsin E occurs. Cathepsin E acts towards many biologically active peptides (Table 9) [67]. The role of cathepsin E in pathobiochemistry is presented in Figure 12 [68].

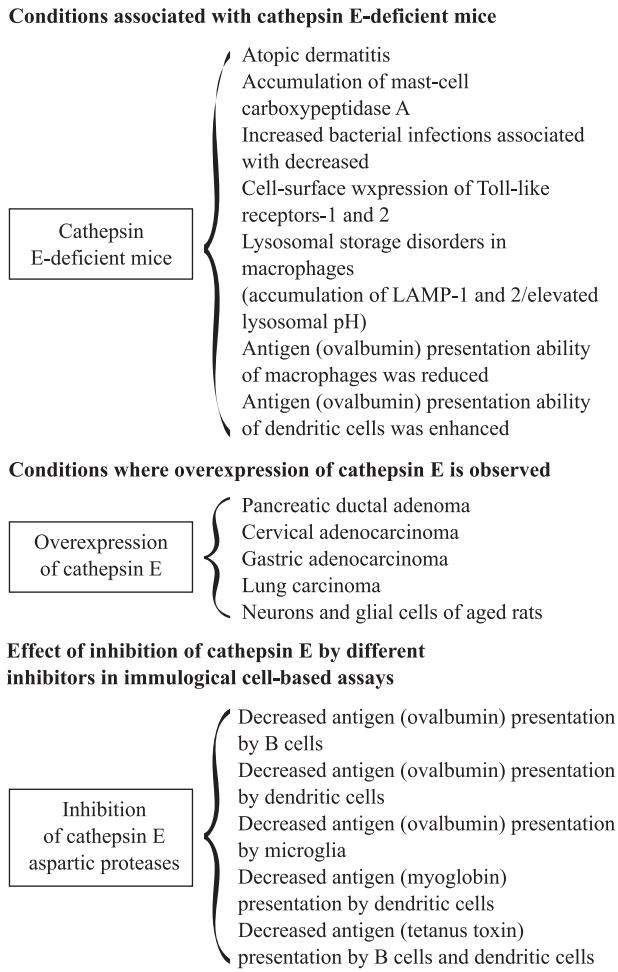

Figure 12. The role of cathepsin E in pathobiochemistry

Mice with a shortage of cathepsin E are often prone to atopic dermatitis. In humans with diagnosed atopic dermatitis, a decrease of cathepsin E activity in blood erythrocytes has also been observed. This may suggest that a shortage of cathepsin E may predispose one to the development of that disease [69].

An increased activity of cathepsin E has been observed in the case of proliferative diseases such as gastric carcinoma or cervical cancer [70–72]. The greatest attention, however, has been given to pancreatic duct adenocarcinoma, in the case of which cathepsin E can be treated as a diagnostic marker [73, 74]. Cathepsin E may be a promising marker in patients with pancreatic duct cancer. However, the invasive character of the method of taking pancreatic juice limits broader use of that method for routine controls.

In recent reports, a connection between cathepsin E and prostate gland cancer has been proved. Cathepsin E

inhibits growth of the tumor and inhibits apoptosis in prostate cancer cells by releasing tumor necrosis factor [75]. Furthermore, inhibition of tumor growth by inhibition of angiogenesis, as well as strengthening immunological response, has been found [76]. An increased activity of cathepsin E in tumors causes increased expression of certain anti-angiogenic factors, including interleukin-12 and endostatin.

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