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Cathepsins: Proteases that are vital for survival but can also be fatal

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ABSTRACT

The state of enzymes in the human body determines the normal physiology or pathology, so all the six classes of enzymes are crucial. Proteases, the hydrolases, can be of several types based on the nucleophilic amino acid or the metal cofactor needed for their activity. Cathepsins are proteases with serine, cysteine, or aspartic acid residues as the nucleophiles, which are vital for digestion, coagulation, immune response, adipogenesis, hormone liberation, peptide synthesis, among a litany of other functions. But inflammatory state radically affects their normal roles. Released from the lysosomes, they degrade extracellular matrix proteins such as collagen and elastin, mediating parasite infection, autoimmune diseases, tumor metastasis, cardiovascular issues, and neural degeneration, among other health hazards. Over the years, the different types and isoforms of cathepsin, their optimal pH and functions have been studied, yet much information is still elusive. By taming and harnessing cathepsins, by inhibitors and judicious lifestyle, a gamut of malignancies can be resolved. This review discusses these aspects, which can be of clinical relevance.

1. Introduction

Cathepsins are protease enzymes, categorized into multiple families. They can be serine protease, cysteine protease, or aspartyl protease [1]. There were about 11 classes of cathepsins in humans [2], which have now increased to 15, as presented in Table 1. These enzymes are active in the low pH milieu of lysosomes and are versatile in their functions. Like other enzymes, they are vital for the normal physiological functions such as digestion, blood coagulation, bone resorption, ion channel activity, innate immunity, complement activation, apoptosis, vesicular trafficking, autophagy, angiogenesis, proliferation, and metastasis, among scores of others [3,4]. Autophagy is a protective process involving lysosomal degradation of misfolded proteins [5,6]. But it becomes an adversary when equilibrium is broken. Numerous pathologies have been attributed to the dysregulated cathepsins, some of which include arthritis, periodontitis, pancreatitis, macular degeneration, muscular dystrophy, atherosclerosis, obesity, stroke, Alzheimer's disease, schizophrenia, tuberculosis, and Ebola.

The structures, distribution, substrate affinity, and the clinical significance of this enzyme family have been reviewed widely [7]. They are expressed on different cells throughout the body such as dermal fibroblasts, among others. The preferences of certain cathepsins on specific cells such as microglia cells, erythrocytes, lymphocytes, macrophages, dendritic cells, lungs, Langerhans cells, epithelium of gastrointestinal tract, urinary bladder, osteoclasts, spleen, thymus, dermal fibroblasts, etc. have been observed. Though a number of cathepsins might be working in tandem or in synchrony for a function, some tissue-specific cathepsins have been reported. For example, Cathepsin E is expressed on a broad range of immune cells [8], cathepsin K on skin fibroblasts [9], and cathepsin L only in the placenta [10]. However, these inferences could be only the limitations of experimental knowledge or even be misleading. A publication reports that Cathepsin L is found in the thymus as well [11]. With changing pH and inflammatory state, the cathepsin expression profiles are likely to be changing.

2. Types of cathepsins and their functional specificities

Cathepsin precursors undergo proteolytic processing and maturation within the lysosomes [12]. All isoforms of the cathepsin exert proteolytic activity, but they favor specific pH. Different pH conditions lead to various protonation states of amino acid residues of the cathepsins. Neutral pH can attenuate cathepsin activity, while alkaline pH can lead to the inactivation of cathepsins [13]. The accurate pH determination of cathepsins is cumbersome, as several factors influence it.

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Table 1
Classes of cathepsins, their protease types, biological roles, and diseases they cause when homeostasis is lost.

No.	Classes of cathepsins	Protease type	Mechanisms	Diseases	Reference
1	Cathepsin A	Serine protease	Processing of endogenous bioactive peptides Inhibit autophagy	Muscular dystrophy Galactosialidosis	[14]
2	Cathepsin B	Cysteine protease	Promotes amyloid plaque Matrix degradation and cell invasion Enable virus entry into the cells	Alzheimer's disease Cancer	[16]
3	Cathepsin C	Cysteine protease	Inflammation Catalyzes the excision of dipeptides from the N-terminus of protein and peptide substrates	Papillon-Lefevre disease Keratosis Periodontitis	[122]
4	Cathepsin D	Aspartyl protease	Mitogen and promotes invasiveness Cleaves ECM proteins	Breast cancer Possibly Alzheimer disease Neuronal ceroid lipofuscinosis (NCL)	[47]
5	Cathepsin E	Aspartyl protease	Antigen processing via the MHC class II pathway	Atopic dermatitis	[8]
6	Cathepsin F	Cysteine protease	Contains five potential *N*-glycosylation sites, and it may be targeted to the endosomal/lysosomal compartment via the mannose 6-phosphate receptor pathway	Type B Kufs disease	[22,24]
7	Cathepsin G	Serine protease	Plays an important role in eliminating intracellular pathogens and breaking down tissues at inflammatory sites, as well as in anti-inflammatory response	Tuberculosis Rheumatoid arthritis Coronary artery disease Periodontitis Ischemic reperfusion injury	[25]
8	Cathepsin H	Cysteine protease	Endopeptidase activity	Prostate tumors Severe myopia Diabetes mellitus type 1	[123]
9	Cathepsin K	Cysteine protease	Cleaves ECM protein collagen Secretion by osteoclasts in bone resorption	Osteoporosis Arthritis Atherosclerosis Obesity Schizophrenia Cancer metastasis	[30]
10	Cathepsin L	Cysteine protease	Matrix degradation and cell invasion Enable virus entry into the cells	Cancer Gingival overgrowth	[33,34]
11	Cathepsin O	Cysteine protease	Collagenolysis Elastinolysis Osteoclastic bone resorption	Cardiovascular disease	[124]
12	Cathepsin S	Cysteine protease	Antigen presentation Remodeling of connective tissue and basement membranes	Type IV astrocytomas (glioblastoma multiforme) Atherosclerosis	[125]
13	Cathepsin V	Cysteine protease	Production of enkephalin and neuropeptide Y	Keratoconus	[126]
14	Cathepsin W	Cysteine protease	Cell-mediated cytotoxicity	Inflammatory bowel disease autoimmune gastritis	[127]
15	Cathepsin Z	Cysteine protease	Protein degradation	Cancer malignancy, inflammation	[48]

Cathepsin B activity is acidic pH-dependent, the pH 5.6 favoring its gelatinase activity. Whereas vesicle-associated cathepsin B showed 1300-fold higher activity at acidic pH values compared to the physiological pH 7.4, the cells extract cathepsin B showed 33-fold higher activity at acidic pH values compared to the physiological pH 7.4 [14]. Cathepsin L has a pH range of 3.5–6. Cysteine cathepsins like B and L are located in the acidic compartments of cells [3].

The protein encoded by SNX10 (Sorting Nexin 10) plays an essential role in endosomal trafficking and chaperone-mediated autophagy [15]. It mediates cathepsin A maturation, playing essential roles in alcohol-induced liver injury and steatosis. Cathepsin A causes the inactivation of bioactive peptides such as bradykinin, substance P, oxytocin, angiotensin I and endothelin-I. The role of this enzyme in galactosialidosis has come forth [16]. Cathepsin A can inhibit autophagy [5,6]. Cathepsin B promotes amyloid plaque [17], and various carcinomas [18]. This enzyme is instrumental in both basal and EGF (epidermal growth factor)-stimulated lung cancer cell migration. Prorenin, the precursor of kidney-secreted hormone renin, can be activated by cathepsin B [19]. Renin-angiotensin-aldosterone system (RAAS) is critical for the homeostasis of plasma sodium concentration, and vascular tonicity *i.e.* blood pressure. RAAS activation underlies numerous pathologies [20]. Cathepsin B from amoeba can cleave several human proteins including immunoglobulins (IgA, IgG, IgM), hemoglobin, collagen, fibronectin, and albumin [21]. Cathepsin D cleaves fibronectin and laminin. A number of breast cancer biomarkers have been identified, among which cathepsin D is one [22]. Cathepsin D can express on desmosomes, the intercellular junctions, causing desquamation [23]. Cathepsin E is frequently implicated in antigen processing via the MHC class II pathway [8]. Cathepsin F has been detected in helminthic pathogens as liver fluke *Opisthorchis viverrini* (known to cause cholangiocarcinoma) [24], as well as hepatobiliary trematodes such as *Clonorchis sinensis*, *Paragonimus westermani*, *Schistosoma mansoni*. *Trichinell a*spp. (known to cause trichinellosis) [25]. Kufs disease, an adult-onset neuronal ceroid lipofuscinosis occurs due to polymorphism in *CTSF* gene, which encodes cathepsin F [26]. The regulatory role of cathepsin in cancer is implicated, but much remains elusive. Lung granulomas where *Mycobacterium tuberculosis* survives, is rich in cathepsin G [27]. Neutrophil extracellular traps (NETs), the conglomerate of DNA, histones, serine proteases (such as neutrophil elastase, cathepsin G), myeloperoxidase (MPO), and proteinase 3 are released from the human granulocytes when an inflammatory signal is perceived [28,29]. NETs attempt to inhibit the pathogens, but the microbial virulence factors such as bacterial nucleases can degrade NET [30]. Cathepsin K is highly effective in degrading collagens [31]. Type I collagen, the major component of the