# 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.

**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<br>Inhibit autophagy | Muscular dystrophy<br>Galactosialidosis | [14] |
| 2 | Cathepsin B | Cysteine protease | Promotes amyloid plaque<br>Matrix degradation and cell invasion<br>Enable virus entry into the cells | Alzheimer's disease<br>Cancer | [16] |
| 3 | Cathepsin C | Cysteine protease | Inflammation<br>Catalyzes the excision of dipeptides from the N-terminus of protein and peptide substrates | Papillon-Lefevre disease<br>Keratosis Periodontitis | [122] |
| 4 | Cathepsin D | Aspartyl protease | Mitogen and promotes invasiveness<br>Cleaves ECM proteins | Breast cancer<br>Possibly Alzheimer disease<br>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<br>Rheumatoid arthritis<br>Coronary artery disease<br>Periodontitis<br>Ischemic reperfusion injury | [25] |
| 8 | Cathepsin H | Cysteine protease | Endopeptidase activity | Prostate tumors<br>Severe myopia<br>Diabetes mellitus type 1 | [123] |
| 9 | Cathepsin K | Cysteine protease | Cleaves ECM protein collagen<br>Secretion by osteoclasts in bone resorption | Osteoporosis<br>Arthritis<br>Atherosclerosis<br>Obesity<br>Schizophrenia<br>Cancer metastasis | [30] |
| 10 | Cathepsin L | Cysteine protease | Matrix degradation and cell invasion<br>Enable virus entry into the cells | Cancer<br>Gingival overgrowth | [33,34] |
| 11 | Cathepsin O | Cysteine protease | Collagenolysis<br>Elastinolysis<br>Osteoclastic bone resorption | Cardiovascular disease | [124] |
| 12 | Cathepsin S | Cysteine protease | Antigen presentation<br>Remodeling of connective tissue and basement membranes | Type IV astrocytomas (glioblastoma multiforme)<br>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<br>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

organic bone matrix, is dissolved by this cathepsin, so this enzyme is essential for normal bone resorption [32]. However, its imbalance causes osteoporosis, arthritis, and cancer metastasis. These bone metabolism anomalies occur due to the degradation of organic matrix by cathepsin K. Cathepsin K also degrades gelatin, the latter being a hydrolysis product of collagen. A study found that the disruption of cathepsin K resulted in defective Toll-like receptor 9 (TLR 9) signaling in dendritic cells [33]. So, the scope of this cathepsin as a therapeutic target in autoimmune diseases was proposed. Polymorphism in the cathepsin K-encoding gene is responsible for pycnodysostosis, an autosomal recessive bone disease [34]. Cathepsin L degrades fibronectin, insulin receptor, and insulin-like growth factor 1 receptor (IGF-1R). Coronaviruses use cathepsin L, apart from angiotensin-converting enzyme 2 (ACE2), to infect humans [35]. Cathepsin L is involved in the biosynthesis of a wide-range of neuropeptides [36]. Among others, enkephalin, β-endorphin, dynorphin, ACTH, α-MSH, NPY, CCK *etc.* are processed by this cathepsin. Cathepsin L deficiency leads to chromatin structure anomaly which is related to its interaction with histones [2]. Some cathepsins, including cathepsin L, are only expressed in the placenta [10]. It is becoming increasingly evident that in cancer progression, not only the tumor cells, but also the cells in its vicinity play decisive role. The microenvironmental stimuli can promote angiogenesis, invasiveness, and proliferation [37,38]. It has come forth that apart from tumor cells, tumor-associated macrophages and endothelial cells can produce cathepsin S, which promotes neovascularization and tumor growth [39]. Cathepsin V (or L2), an elastase, is involved in cancer invasion and metastasis as well [40].

Cathepsins K, L, S, F, V, and B possess elastolytic activities and are reported to be responsible for the stiffening of arteries in atherosclerosis [41,42]. Cathepsins B and L promote the cell entry of paramyxoviruses, reovirus [43–45], and Ebola virus, among others [46], by activation of their glycoproteins. Cysteine cathepsins are also upregulated during human papillomaviruses HPV16-induced cervical carcinogenesis [47]. Microglia-expressed cathepsins B, D and S have been implicated in the pathogenesis of Alzheimer's disease [7]. The impaired activity of *CTSB* (cathepsin B) and *CTSD* (cathepsin D) genes cause saposin C-deficient fibroblasts, and the accumulation of autophagosomes, leading to a form of lysosomal disorder, the Gaucher disease [48].

The physiological role of cathepsin H, O, W, and Z have so far been only sparsely characterized. Cathepsin Z promotes tumor proliferation via the Arg-Gly-Asp (RGD) motif in its prodomain, which interacts with integrins and the ECM [49]. The functional profiles of the cathepsins are constantly evolving; new functions are being assigned to them, and functional overlapping between different cathepsins are being observed.

## 3. Mechanisms of cathepsin-driven pathogenesis

Extracellular matrix (ECM) consists of a multitude of proteins (elastin, fibronectin, laminin, collagen, platelet-derived growth factors (PDGFs), transforming growth factor ß induced protein (TGFBIp)) [50], proteoglycans (biglycan, perlecan, versican *etc.*) [51], glycoproteins [52,53], and host-derived extracellular RNA (eRNA), among a scores of other known and unknown components. ECM, apart from providing support to the tissues [53], is critical for tissue integrity, gene expression, and immune homeostasis, among other functions. The activated proteases such as metalloproteinases (MMPs), and other proteases degrade ECM and lead to its remodeling [53–55]. ECM breakdown products act as damage-associated molecular patterns (DAMPs) for the activation of NLRP3 inflammasomes [56]. Cathepsins degrade low-density lipoprotein (LDL-P) and attenuate cholesterol efflux from macrophages, leading to foam cell formation [55]. The foam cells are responsible for atherosclerosis and coronary artery disease. Fibrosis and cancer, among other inflammatory diseases, are the resultant of perturbed ECM [50].

Galectin is a β-galactoside-binding, regulatory protein, with role in cell adhesion, cell cycle control, immunomodulation, and cancer progression [57]. Its isoform 1 and 3 have different functions, which occur by their lectin property. *i.e.* they recognize ECM matrix glycans. Galectin-3 causes T cell and dendritic cell regulation, and mast cell apoptosis [58]. Its expression is high in tubular carcinoma, up-regulating the expressions of protease-activated receptor-1 (PAR-1) [59]. Galectin-3 is a target for microbial proteases [60]. Ceramide, a sphingolipid, a lipid second messenger, elicits cellular stress response and controls autophagy. It induces autocatalytic proteolysis of pre-pro cathepsin D to cathepsin D [61].

E-cadherin is a target substrate of cathepsins B, L, and S [62]. Cadherin proteins mediate cell-cell adhesion and synapse control. Cadherin domain in cadherins, is one of the handful of pathogenically-dominant protein domains [63–65].

The glycosylation state of cathepsin determines its functionality. In an *in vitro* study, *N*-glycosylation of cathepsin V at Asn221 and Asn292 was found crucial for the transportation to lysosome, and secretion [66]. The glycosylation is dominated by high-mannose-type sugars [67].

Cathepsins and other proteases are equipped to degrade microbial peptides. As the proteases are also likely to ravage host tissues, their cognate antiproteases, the peptides, are expressed as well [68], which is discussed in details in the following section. If the protease production is perpetual, the antiproteases are produced persistently as well. Though the peptides are meant to block the protease activity, excess peptides itself are lethal for the body. Together they maintain a state of inflammation.

## 4. Cathepsin inhibitors

It has been consistently observed that inhibitors can block cathepsin function, which can prevent tumorigenesis, angiogenesis, tumor cell motility, and invasiveness, among other pathologies. The inhibitors can be of endogenous, or exogenous origin, and are natural or synthetic. The section below outline some cathepsin inhibitors. Antimicrobial peptides (AMPs) are amphiphilic molecules of 'defense and offense' functions [69]. AMPs are present in all living organisms, and they protect the host by eliciting immunogenicity against other organisms [69]. Hevein, an AMP in the latex of *Hevea brasiliensis* (rubber plant) have the chitin-binding domains (ChtBDs) [70–72]. Other plant AMPs of pathogenic relevance include knottins, which encompass lectins, amylase inhibitors, and thionins, among others [69]. Arthropod AMPs like formaecin, drosocin, apidaecin, abaecin, metchnikowin, lebocin, pyrrhocoricin and metalnikowin are proline-rich [73]. Predominant AMPs in humans include defensins, cathelicidins, histatins *etc.* [74–76]. Several of the AMPs are inhibitors of proteases, including the cathepsins [77]. Cystatin family AMPs, which encompass statherins, histatins, and proline rich proteins (PRPs), and they can inhibit cathepsins B, H and L *etc.* [78]. Stefin B or cystatin B inhibits cathepsin L [79] as well as other proteases [80]. Histatins in saliva inhibits pathogenic fungi *Candida albicans* by binding to the fungal cell wall proteins and glycans, subsequently being internalized by fungal polyamine transporters, imposing oxidative stress, and hampering mitochondrial functions, perturbing ionic balance and eventually killing the fungi [76]. Kininogen, another cystatin-related protein, a kinin precursor, has cystatin domains which can inhibit cysteine cathepsins [81]. Tasiamide B, a cyanobacterial peptide with a statin-like unit, inhibited cathepsin D and other aspartic proteases [82]. Cathepsin D activity is inhibited by α2-macroglobulin [83]. This glycoprotein contains a receptor-binding domain, and is a major and broad spectrum protease inhibitor in the human body [83,84]. Cathepsins are competitively inhibited by glycosaminoglycans (dermatan sulfate and hyaluronan) [85]. A major glycosaminoglycan, chondroitin sulfate, inhibited cathepsins K and V, by forming complex with these proteases [41]. A study found that the removal of collagen-associated glycosaminoglycans prevented cathepsin K binding and subsequent collagen hydrolysis [31].
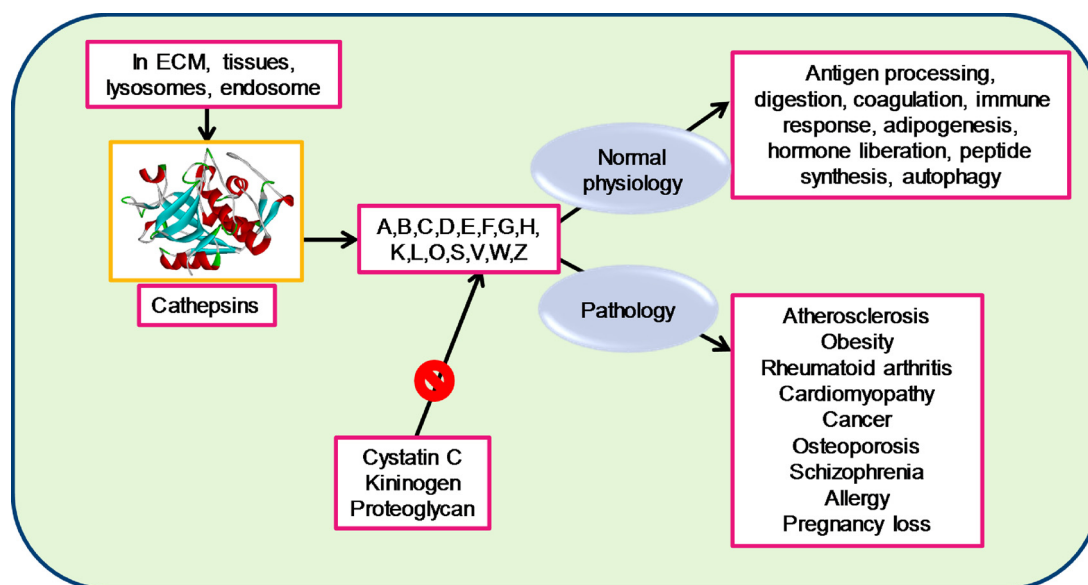
**Fig. 1.** Cathepsins are necessary evils, like other proteases. They are present in extracellular matrix, lysosome, melanosome. In normal physiological condition, they play role in digestion, coagulation, immune response, adipogenesis, hormone liberation, peptide synthesis, autophagy. But, in inflammatory condition they can pave the path for cancer, cardiac disease, arthritis, pregnancy loss, among other diseases.

E-64, an epoxide, isolated from *Aspergillus japonicus*, and its derivatives can inhibit cathepsin [80,86]. Epoxide-containing fungal metabolites serving as antiangiogenic agents have been reported previously. *Yersinia enterocolitica* strains synthesize cathepsin L inhibitors [87]. Plant and animal-derived flavones have demonstrated their cathepsin-inhibitory property [87]. Flavone from rice bran tricin (5,7-dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-4H-chromen-4-one), and propolis chrysin (5, 7-dihydroxyflavone) have different extent of antiproliferative properties [88–90]. Biflavones have proven to be the reversible inhibitors of cathepsin B [91]. A flavonoid 3′,4′,7,8-tetra-hydroxyflavone from *Acacia confusa* inhibited receptor activator of nuclear factor kappa B ligand (RANKL)-induced osteoclastic differentiation, by lowering the mRNA expression levels of cathepsin K [92]. Acridone alkaloids from *Swinglea glutinosa* could reversibly inhibit cathepsin V by competitive inhibition [93].

Compounds with pyrimidine scaffold are effective as cathepsin inhibitors. Pyrrolopyrimidine-based inhibitors could inhibit cathepsin S, K and L [94]. *N*-Formylpyrazolines possessed superior inhibitory effect than *N*-benzoylpyrazolines. Odanacatib, an experimental cathepsin K inhibitor, can offer recovery in bone fractures [95]. Its selectivity and half-life was better than other cathepsin K inhibitor balicatib and relacatib [95]. Five cyclic peptides showed cathepsin inhibitory activity. Cathepsin B was blocked by Ca-074Me (a methyl ester derivative of CA-074), which resolved the activation of NLRP3 inflammasomes [96]. Cathepsin D inhibitors include chemicals which esterify carboxyl groups of the Asp33 and Asp231 residues at the enzyme's catalytic sites [97].

The MEROPS database has a comprehensive list of cathepsin inhibitors [98]. Testican, amoebiasin, toxostatin, asteropterin, nitroxoline, clitocypin, falstatin, macrocypin, gallinamide A, leupeptin, allicin, and equistatin are some of the cathepsin inhibitors which belong to diverse chemical families as proteoglycans, proteins, organosulfur compounds, among others.

## 5. Discussions

The physiological pH range prevents the activation of protease, glycosidase, urease, phospholipase, cyclooxygenase, aromatase, ATP synthase, and a whole array of other enzymes [99,100]. Low pH converts the pro-enzymes to their active forms. As low pH activates the enzyme, tissue remodelling, and gene expression changes occur, which pave the path for tumorigenesis [50]. Cathepsin-containing vesicles are expressed on cell surfaces. There are several approaches which can prevent the activation of cathepsins. Avoidance of infections, allergens, chemical cosmetics, processed foods, and pollutants can restore the normalcy of cathepsin level and function. The mechanism underlying the aberrant activation of cathepsins due to inflammation driven by above-mentioned factors has been explained briefly. Acidogenic attribute of modern foods are well-known. They might be tongue-tasty or easy-to-prepare, but they provoke pH fall, and abnormal enzyme activation. Acidosis induces MAPK (mitogen-activated protein kinase) phosphorylation [101], and activates proton-sensing proteins (G-protein-coupled receptor (GPCR) as OGR1, GPR4, and TDAG8) which impedes actin polymerization/depolymerization [102,103]. Ion channels as the proton-gated sodium channels are manipulated, and the ionic perturbation leads to pain [104–106]. Perceiving that stressors are around, efflux proteins such as P-glycoprotein (P-gp) are expressed [107–110]. The healthy aspect of Paleo diet, dominated by unprocessed foods, acts as a buffer towards pH fluctuation [111]. The ingestion of Nordic diet decreased cathepsin S levels in healthy individuals, by lowering LDL cholesterol [112]. Oral supplementation of *Lactobacillus reuteri* and *Lactobacillus gasseri* strains reduced the expression of cathepsin L in mice muscles, indicating decreased inflammatory cytokines such as IL-6, monocyte chemo-attractant protein-1, and IL-4) [113].

The diverse cathepsins share one parent protease. Evolution has led to amino acid substitutions and functional diversities. Accordingly, their tissue distribution varies.

Plant pollens contain subtilisin-like serine proteases, which can disrupt human cell membrane permeability by manipulating trans-membrane tight junction proteins such as occludin, claudin-1, ZO-1 and E-cadherin [114,115]. It has been previously mentioned that E-cadherin is a target of certain cathepsins [62]. So, cathepsins play role in allergenicity.

Cathepsin inhibitors can prevent the viral entry into host cells. AIDS drugs include HIV protease inhibitors [116]. It suggests that the inhibitors basically target the proteases, cathepsins or not. Cathepsin is a key member in pathogenesis, but it is not the only one. Its homologs or analogs include other serine proteases such as trypsin, thrombin, subtilisin, chymotrypsin, elastase, collagenase, and kallikrein. Together they control digestion, blood coagulation, immune regulation, protein

metabolism, autophagy and apoptosis, among numerous other functions [5,117–119]. Apart from the autocatalysis of cathepsins, these proteases play role in the activation of cathepsins.

Cysteine cathepsin has shown co-expression with MMP in human dentin-pulp complex. MMPs, which encompass numerous members, have been implicated in pathologies such as arthritis, atherosclerosis, ulcers, periodontal disease, fibrotic lung disease, multiple sclerosis, liver cirrhosis, endometriosis, pulmonary emphysema *etc.* [120]. Human macrophage chitinase facilitates tissue remodeling [121]. However, all of the above-mentioned enzymes are capable of destroying ECM integrity. A number of proteases increase vascular permeability by activating plasma kallikrein-kinin system [122] and renin-angiotensin-aldosterone system [20]. These system activations generate vasoactive agents like bradykinin and angiotensin II, respectively.

Fig. 1 presents the actions of different cathepsins in normal physiological conditions and pathological milieu.

## 6. Conclusion

Cathepsins can wreak havoc with the human body, but only if the body pH is below the physiological level *i.e.* if acidosis prevails. In other words, cathepsins are vital for survival. They multitask, moonlight, and mediate diverse essential functions. Cathepsins can turn evil, if human body becomes acidic, hypoxic, and inflammatory. It is no wonder that the dysregulation in their functions is the hallmark of cancer, infertility, bone loss, and neural diseases. Therapy aimed at their normalcy restoration may or may not be effective, given the complexity of human system and the unpredictable behavior of immune system in an inflammatory milieu. So, an attempt to not incite the activation of the enzymes, by adhering to healthy, non-inflammatory lifestyle, is suggested.

## Conflict of interest

There is no conflict of interest in submission of the manuscript.

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