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TITLE: ROLE OF CATHEPSIN IN ORAL DISEASE – A review

Authors:
[1]Dr. Lalli Dharmarajan, [2]Dr. E.P. Sridevi Anjuga, [3]Dr. Pradeep P Elango, [4]Dr. N. Aravindha Babu MDS

Molecular biologist, Centre for Oral Cancer Prevention Awareness and Research, Sree Balaji Dental College & Hospital, Chennai.BIHER
Post Graduate student, Department of Oral pathology & Microbiology, Sree Balaji Dental College and Hospital, Chennai. BIHER.
Assistant Professor, Dental Department, Dhanalakshmi Srinivasan Medical College and Hospital.
Professor, Department of Oral Pathology & Microbiology, Sree Balaji Dental College & Hospital, Chennai, BIHER

ROLE OF CATHEPSIN IN ORAL DISEASES – A REVIEW:

ABSTRACT:
Cathepsins are a class of globular lysosomal proteases that are known to be responsible for protein degradation. They have many biological roles besides proteolysis, such as apoptosis wound healing angiogenesis, proenzymatic activation, bone remodeling, and resorption. The role of cathepsins in pathogenesizing systemic diseases such as cancer, bronchial asthma, atherosclerosis, neurological disorders, rheumatoid arthritis and osteoarthritis has been involved. This review emphasizes the role of cathepsins in multiple oral diseases such as periodontitis, odontogenic cysts, ameloblastoma, tumors of the salivary glands and malignant melanoma.

KEYWORDS: Cathepsin, Oral disease, Proteases, cancer

1. INTRODUCTION:

Proteases are the type of enzymes that catalyze hydrolysis of peptide bonds and aid in the digestion of proteins. These enzymes are pervasive in nature, and control many biological processes[1]. They control blood clotting, cell proliferation, angiogenesis, wound repair, necrosis, and apoptosis[1]. There are 84 families of proteases that are categorized by their catalytic activity into serine, aspartic, cysteine, and metalloproteases[1]. The name cathepsin, which is derived from the Greek kathepsein (to digest), was proposed for the protease that was active in a slightly acidic environment[2].Later, Rich Willstaetter and Eugen Bamann proposed the terminology "cathepsin" in 1929 to describe the tissue proteolytic activity of leucocytes at a slightly acidic pH[1]. Cathepsins are graded as:

1. Serine proteases: cathepsins A and G;
2. Aspartic proteases: D and E cathepsins; and lysosomal cysteine cathepsin
3. There are 11 human cysteine cathepsins, i.e., the cathepsins B, C, F, H, K, L, O, S, V, X and W, existing at the sequence level; this was confirmed by a bioinformatic analysis of the draft sequence of the human genome[2].

Such enzymes play a key role in multiple physiological processes such as apoptosis, antigen presentation, activation of proenzymes, wound healing, bone remodeling, neuropeptide, and storage of hormones[1]. The expression of cathepsins is regulated by endogenous inhibitors such as cystatins, serpins, and thyropins to preserve tissue homeostasis[2]. The release of inactive cathepsins and the presence of endogenous inhibitors help to maintain physiological equilibrium[1]. Numerous ailments such as atherosclerosis, osteoporosis,

arthritis, neurological disorders and cancer have been connected with their dysregulation[1]. Cathepsins are also produced by pathogenic bacteria which act as virulence factor and result in development of diseases[1].

2. STUCTURE OF CATHEPSIN:

The crystal structure of papain, a cysteine protease from Carica papaya, was among the first dozen protein crystal structures to be determined. Together with actinidin, these two structures provided the first insight into their three-dimensional (3D) structure. Later developments enabled the isolation of cysteine cathepsins, such as cathepsin B, H, L, S, X, C, from various tissues, while the rest of the cathepsins were expressed in various expression systems[2].

3. CATHEPSIN STRUCTURE ACTIVATION AND INHIBITION:

The cathepsins are produced as inactive zymogen; the prodomain found in zymogen blocks the active sites, preventing hydrolysis of the substrates[3]. Zymogen change is necessary for activation, in which the prodomain is removed[3]. The signal peptide present in inactive state is cleared inside the endoplasmic reticulum and these proenzymes are glycosylated, which are then carried to Golgi apparatus[2]. Phosphorylation of mannose residues occurs in Golgi apparatus, and mannose 6 phosphate is produced which reaches lysosomes through mannose 6 receptor pathway[3]. Acidification occurs in late endodosome resulting in disassociation of prodomain from active site and becoming active in cathepsins[3]. Therefore, Prodomain serves as an autoinhibitor for cathepsins[3]. The entire activation takes place through autocatalytic or transactivation mechanisms in the lysosomes[3]. Activation process is enhanced by acidic condition and presence of glycosaminoglycans. Proteolytic activation is mediated by metalloproteinases in the matrix[3].
Cathepsin activity can be controlled mainly by distortion and blockage of active site by inhibition[1]. Endogenous inhibitors including cystatins, thyropins, and serpins suppress cathepsin[1]. Cystatins form the largest group of endogenous cathepsin inhibitors that primarily target cysteine proteases[4]. Intracellular cystatins inhibit cysteine proteases by slightly blocking the active center by noncovalent interaction[4].
The cystatine family is further divided into:

- cystatin type 1 (stefins),
- cystatin type 2 (cystatins), and
- cystatin type 3 (kinogens).

The serpins can inhibit serine proteases and cysteine proteases[4]. Its inhibitory mechanism is by active site degradation[4]. Thyropins suppress the proteases in cysteine. There are no known endogenous aspartate protease inhibitors till date[4].

4. CATHEPSIN LOCALIZATION AND FUNCTION:

CATHEPSIN B:

Cathepsin B is the first identified member of what has become known as the broad family of lysosomal cysteine peptidases[5].This is the most widely expressed cathepsin encoded by the CTSB gene mapped by chromosome 8p22[1]. It is present at high levels in gingival crevicular fluid and macrophages[1]. Cathepsin B was immuno-localized to granular duct cells and gingival fibroblasts in the submandibular gland[1]. This is active primarily in cellular processes such as proteolysis, antigen synthesis, and apoptosis[1]. Cathepsin B is an essential activator of trypsin in acute pancreatitis[3]. It also causes collagen degradation and other non-collagenous matrix proteins, and thus plays a key role in resorption lacunae formation in deciduous teeth[6]. It can be seen in the human dentin- pulp complex [1]. Cathepsin B was identified also in ameloblasts[1].

CATHEPSIN C:

Cathepsin C (CTSC), also known as dipeptidyl peptidase I, is encoded by the CTSC gene located on chromosome 11q14[7]. It is an exogenous salivary peptidase that extracts dipeptides away from N-terminals peptides[7]. In inflammatory cells, it plays a major role in activating platelet factor XIII and various serine proteases[7]. Increased levels of enzymatically active serine-cysteine cathepsin-C were expressed by dermal / stromal fibroblasts and bone marrow-derived cells, which controlled the complexity of infiltrating immune cells in neoplastic skin, angiogenic vasculature development and overt squamous cell carcinoma growth[8].

CATHEPSIN D:
Cathepsin-D is a proteinase that induces collagenolytic activity, resorption of the bone and is closely involved in tumor progression biological process[9]. Cathepsin-D was present in many normal tissues, including epithelium, fibroblast, and macrophages[9]. Cathepsin-D 's physiological function is thought to be involved in the self-destruction of senescent or weakened epithelial cells[9]. Cathepsin D is involved in protein, polypeptide hormone and growth factor metabolic degradation[10]. It functions as mitogen in many epithelial tissues and helps in remodeling and renewal of tissue[10]. It is present in the gingival fluid in the oral cavity and immuno-located in rat junctional epithelium and oral mucosa[10].

CATHEPSIN G:
It is mainly formed by neutrophils and plays an important role in the elimination of intracellular pathogens and the breakdown of tissues at inflammatory sites[1]. In addition, it is involved in platelet activation that leads to platelet aggregation and formation of clots[1]. CTSG has been found in other myeloid cells, such as B cells, primary human monocytes, dendritic myeloid cells, dendritic plasmacytoid cells and murine microglia[11]. Cathepsin G has a number of functions. It can clear pathogens, regulate inflammation, stabilise blood pressure, and induce thrombogenesis by altering chemokines, cytokines, cell surface receptors and C components[11]. The concentration and activity of CTSG are increased in the synovial fluids of rheumatoid arthritis (RA) patients[11].

CATHEPSIN K:
This protein, a part of lysosomal cysteine proteases, mainly expressed in osteoclasts and is involved in bone remodelling and resorption. It can break down bone and cartilage through its catabolic action[1]. Cathepsin K found in the odontoclasts in the deciduous tooth is responsible for the extracellular degradation of dentin collagen during physiological root resorption[1]. In rheumatoid arthritis joints, cathepsin K is strongly expressed in osteoclasts, in most epithelial cells, and in synovial fibroblasts[2]. Cathepsin K is the only enzyme that has been unambiguously recorded in mice and humans to play an important role in bone resorption[2].Cathepsin K was also highly displayed in patients suffering from ankylosing spondylitis at bone destruction sites[11]. Cathepsin K contributes both to the erosion of the blood vessels and to plaque destabilization[12]. Cathepsin K inhibitors are useful tools for adipogenesis and analyse the role of cathepsin K in obesity, and may represent potential for future treatment[12]. Cathepsin K has also been suspected in pathogenesis of osteoarthritis[12]. In addition to its expression in breast, lung, melanoma and thyroid cancers, cathepsin K has also been associated with increased invasive potential in prostate tumours[12].

CATHEPSIN L:
Cathepsin L is implicated in the cleavage of a broad variety of compounds, such as fibronectin, collagen and laminin, including the extracellular matrix[10]. Cathepsin L is believed to be involved in intracellular or endocytosed protein turnover, antigen processing and presentation, bone resorption, and various other processes[10].

CATHEPSIN S:
Importantly, cathepsin S is expressed in professional antigen-presenting cells (APCs), such as dendritic cells (DCs) and B-cells[2]. It is a lysosomal cysteine protease capable of degrading extracellular matrix components, such as collagen, elastin, fibronectin, laminin, and proteoglycans, which indicate a pivotal role in homeostasis and repair of tissue[13]. Cathepsin S facilitates cell migration and also controls differentiation of osteoblasts and remodelling of bones[13]. Cathepsin S has been widely involved in health and pathology including including autoimmune disorders, allergic inflammation and asthma, diabetes and obesity, cardiovascular and respiratory disorders, as well as cancer[13].

CATHEPSIN W:
Cathepsin W is mainly found in CD8 + lymphocytes and natural killer (NK) cells[2].

CATHEPSIN L:

Cathepsin L variants localized to the nucleus play a role in the regulation of cell-cycle progression[2].Cathepsin L involved in transduction of cardiac signal[3].

CATHEPSIN V:

- Cathepsin V (also called L2) is strongly homologous to cathepsin L but its expression is limited to thymus and testis in contrast to the omnipresent cathepsin L[2]. Specific expression of cathepsin V in human thymic cortical epithelial cells[14]. In stenotic aortic valves and atherosclerotic plaques, the expression of cathepsin V is increased, indicating a role in the degradation of elastin laminae in diseased blood vessels[14]. Cathepsin V was considered a possible diagnostic marker for colon tumours which was identified as an antigen in breast cancer patients[14].
- In patients with multiple sclerosis, the expression and activity of cathepsin B, cathepsin D, and cathepsin S was increased and correlated with the physiological degradation of myelin basic protein[11].
- Cathepsin B and Cathepsin S also had a potential role in the pathology of grave's disease and myasthenia gravis[11].

5. CATHEPSIN IN ORAL DISEASES:

DENTAL CARIES:

- Dental caries is a microbial disease caused by demineralization of inorganic and dissolution of organic matrix[1]. MMPs are primarily involved in the pathogenesis of caries[1]. Cysteine cathepsins are colocalized and thought to activate the latent MMPs and facilitate the development of caries with MMPs[1]. Compared to sound dentin, cathepsin B demonstrated greater immunoreactivity in carious dentin[1]. Cathepsin B levels were associated with rising depth in carious dentin[1]. In the dentinal fluid, MMP-20, MMP-2, and probably also cathepsin B are present and can contribute to the lesion activity in areas with large dentinal tubules[15].

PERIAPICAL LESIONS:

- As a sequelae of pulpal inflammation periapical lesions form around the tooth apex[1]. They manifest as a result of host immune response against bacteria. It may result in resorption of hard tissues and destruction of periapical tissues[1]. Often, some inflamed tissue factors may contribute to the failure of endodontic therapy[1]. Osteoclasts play a key role in deteriorating the bone matrix in periapical lesions[1]. Cathepsin K is primarily expressed in osteoclasts and involved in bone remodelling and resorption[12]. Cathepsin K was a vital bone-resorbing protease and the race for the treatment of osteoporosis was to produce highly selective cathepsin K inhibitors[12].

ORAL LICHEN PLANUS:

- Oral lichen planus is a chronic T-cell- mediated mucosal disease. In psoriasis, cathepsins K in inhibitor has shown to inhibit TLR-mediated cytokine by dendritic cells[16]. TLR4 and TLR9 induction occur in oral lichen planus, and co-expression of cathepsin K has been seen in some dendritric cells[16]. It is therefore proposed that in oral lichen planus, cathepsin K is involved in dendritic cell upregulation of the activity of cytokines[16]. In OLP lesions, epithelial cells under the influence of the underlying stromal proteases of the connective tissue, secreted by the inflammatory cells stained by Cathepsin B, are more likely to turn into cancer cells[17].

PERI-IMPLANTITIS:

- The peri-implantitis inflammatory process affects the tissues surrounding dental implants, sometimes contributing to implant failure[1]. Yamalik et al . noted that cathepsin K operating levels are higher in peri-implantitis and peri-mucositis compared to healthy peri-implant tissues[1]. Increased RANKL expression stimulated the formation of active osteoclasts leading to increased cathepsin K development leading to bone resorption[1].

PERIODONTITIS:

- Periodontitis is a chronic inflammatory disease that is highly prevalent and is characterised by bone, attachment, and even tooth loss[13]. Cathepsin S expressed in periodontitis stimulates the proliferation and migration of PDL cells and thus wound closure, suggesting that this cysteine protease may play a critical role in the healing and periodontal remodelling[13]. Another member of the cathepsin family, Cathepsin K was also associated with periodontal diseases[13]. Cathepsin S is interestingly capable of degrading Cathepsin K, suggesting complex interactions between both cathepsins[13].
- Cathepsin G also showed increased involvement in adults periodontitis[18]. Through proteolytic activation of latent neutrophil procollagenase (promatrix metalloproteinase 8), this enzyme may break down periodontal tissues directly and indirectly and can contribute to periodontitis[18]. As these enzymes correlate with pocket depth, they can serve as biomarkers of periodontal inflammation[18].

6. PAPILLON – LEFEVRE SYNDROME:

It is an autosomal recessive disorder characterised by severe early-onset periodontitis and palmoplantar hyperkeratosis that results in premature loss of teeth. This condition is responsible for mutations within the CTSC gene[1]. CTSC plays a predominant role in phagocytosis[1]. Immunological findings such as reduced neutrophil, monocyte chemotaxis, impaired phagocytosis, and altered superoxide production are noted in patients affected by this syndrome[1]. The cell ability of polymorphonuclear leukocyte (PMNL) does not remove the Aggregatibacter actinomycetemcomitans that result in periodontitis[1].

GIANT CELL TUMORS:

- The giant cell tumour is a benign bone neoplasm marked by localised osteolysis[1]. Cathepsin K is detected exclusively in osteoclast-like giant cells in giant cell tumours which support the hypothesis that it is the predominant factor in osteolysis[1]. Cathespin K staining patterns were large in giant cell lesions in 85% of peripheral giant cell granulomas, 60% of giant cell tumours, and 57% of core giant cell granulomas[1]. Cathepsin L is other protease present in giant cell lesions and tumors[1]. Cathepsin D plays a role in numerous physiological and pathological procedures, including bone resorption[19]. Cathepsin D has been observed in the giant cells of both CGCG and PGCG lesions[19]. The osteoclastic origin of giant cells in both PGCG and CGCG could be confirmed by the expression of Cathepsin D in giant cells, which is considered a factor involved in bone degradation and one of the enzymes present in osteoclasts[19].
- Cathepsin D plays an indirect role in the degradation of the bone matrix through activation of Cathepsin B and L in osteoclasts[19]. Therefore, a higher Cathepsin D concentration in CGCG giant cells may be considered as a factor in developing more active Cathepsin B and L, and therefore more degradation of the bone[19]. Active cathepsin B and L will prevent further osteolytic activity in the lesion[19].

ODONTOGENIC CYSTS AND TUMORS:

- The staining intensity of cathepsin D between various odontogenic cysts was observed in each layer and stroma / capsular wall[1]. In the epithelial lining and stroma, different staining patterns were observed. The staining severity increased gradually from the dentigerous cyst to the odontogenic keratocyst (OKC) via the radicular cyst[1]. This increasing pattern of expression seemed to correlate with increasing aggression[1]. Intense granular staining has been found in OKC's separation region. This finding indicates that cathepsin B may be one of the essential enzymes in epithelium and connective tissue separation in OKC[1]. Marked staining of the granular cells and spillage in granular cell ameloblastoma compared with others may explain its aggressive behaviour, recurrence, and metastatic potential[1].
- Cathepsin-D is a proteinase that induces collagenolytic activity, bone resorption and is closely involved in the biological tumour progression process that has been documented to be an indicator of aggressive behaviour in human tumours, including oral squamous cell carcinoma, due to its ability to digest the extracellular matrix[9] It is suspected that cathepsin-D physiological function is involved in the self-destruction of senescent or weakened epithelial cells[9].
- Cathepsin D is expressed in the epithelium, connective tissue and stromal cells of odontogenic cyst and tumors[9].

SALIVARY GLAND TUMORS:

- Among head and neck tumours, salivary gland tumours are histologically the most heterogeneous tumours. Higher expression of cathepsin D in neoplasms with malignant salivary gland compared to benign tumours. Intense expression of cathepsin D was observed in mucoepidermoid carcinoma and adenoid cystic carcinoma when compared to pleomorphic adenoma, indicating that it was a marker of invasive potential and aggressive behavior[20].

SJOGREN'S SYNDROME:

- Cathepsin B, cathepsin D, and cathepsin S were present in Sjögren's syndrome and had greater immunoreactivity in patient's acini and tears[11]. The cathepsin S inhibitor was effective in the prevention of salivary and lacrimal autoimmune lesions in patients with Sjögren's syndrome[11].

ORAL CANCER:

- Cancer is a multi-stage phase involving genetically altered changes. Diverse proteases monitor the invasiveness and metastasis. Cathepsins degrade the extracellular matrix and thus interrupt intercellular communication.
- Cathepsin B can contribute to uncontrollable proteolysis and participate in the process of tumor development, invasion, and metastasis in dissolution and remodeling of the connective tissue and basement membrane[1]. The expression of Cathepsin B was associated with positive lymph node metastasis and a higher tumor grade, thereby indicating its role in malignant tongue cancer progression[1].
- On the other hand, although Cathepsin C is up-regulated during carcinogenesis of the pancreatic islet, it lacks functional significance in mediating neoplastic progression in that organ[8]. Since the expression and enzymatic activity of both of both Cathepsin B and Cathepsin C are raised in various tumors[8]. Increased levels of enzymatically active Cathepsin C were expressed by dermal / stromal fibroblasts and bone marrow-derived cells, which regulated the complexity of infiltrating immune cells in neoplastic skin, angiogenic vasculature formation, and overt squamous cell carcinoma growth[8].
- The expression of cathepsin D was observed during the conversion of dysplasia to oral squamous cell carcinoma[17]. The expression associated with invasiveness and progression of cancer. The origin of cathepsin D from the lysosome to the invasive front of the tumour is altered and its expression is associated with abnormalities of the p53 gene[17]. Cancer cells also secrete procathepsin D that acts as a metastases and mitogen stimulating proinvasion[17].
- Majority of cancers including a few dysplastic areas surrounding carcinoma tissue, cathepsin K was found in OTSCC patient samples[21]. In the morphologically normal-looking tongue epithelium, we were not able to detect cathepsin K[21]. Cathepsin K was present in carcinomas, as well as stromal cells[21].
- Overexpression of cathepsin L is more likely to lead to progression of tumor in oral cancer[1]. Cathepsin L expression associated with metastasis of the lymph node and poor prognosis, indicating its function as a potent biomarker for cancer prognosis[1].

4. CONCLUSION:

Cathepsins play a vital role in pathogenesis of both systemic and oral diseases. They can act as biomarkers in various oral diseases. Future research and investigation is needed to have a clear idea about the correct pathogenesis of cathepsins in oral diseases.

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