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LYSOSOMAL ENZYMES

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ABSTRACT

Lysosomal enzymes are implicated in tissue remodeling and in regulating the immune responses. Lysosomal enzymes can be incorporated into the explanation of mechanisms of development of various diseases and give scientific grounds for prevention of inflammatory disease. This review highlights synthesis, functions and regulation of lysosomal enzymes.

Key words: Phagocytosis, endocytosis, acid hydrolases, lysosomes, alpha1 –antitrypsin

INTRODUCTION

Lysosomes are small intracellular organelle present in all animal cells. They destroy any foreign material which enters the cell such as bacteria or virus. Lysosomes also remove the worn out and poorly working cellular organelles by digesting them to make way for their new replacements. Since they remove cell debris, they are also known as scavengers, cellular housekeepers or demolition squads. Lysosomes form a kind of garbage disposal system of cell. During breakdown of cell structure, when the cell gets damaged, lysosomes burst and the enzymes eat up their own cells. So, lysosomes are also known as suicide bags of a cell. The major function of lysosomes and lysosomal proteases is not to kill the cell but to take care of cellular homeostasis and possibly differentiation by recycling cellular components.[1]

The release of lysosomal enzymes are normally intended to degrade ingested microbes, could also lead to tissue destruction and amplification of inflammatory response with continued recruitment of new leukocytes. Altered lysosomal membrane stability leads to release lysosomal hydrolases, ensuing altered metabolism of different connective tissue constituents including collagen and also involved in the destruction of non - collagenous components of the extracellular matrix. Hence the present study is designed to give precise account on lysosomal enzymes, may open up new horizons in the research field.[2]

Synthesis of lysosomal enzymes

More than 50 hydrolases involved in the lysosomal degradation of protein, carbohydrate, lipids and nucleic acids have been identified. The hydrolases are enclosed by a membrane containing a set of highly glycosylated lysosomal membrane proteins. The targeting of acid hydrolases depends on the presence of mannose-6-phosphate (M6P) residues that are

recognized by specific receptors mediating the intracellular transport to an endosomal or prelysosomal compartment. The lysosomal apparatus is responsible for the intracellular digestion of externally and internally generated macromolecules. Coated vesicles internalize most extracellular macromolecules by endocytosis to form early endosomes, which move from the plasma membrane towards the cell nucleus. They become acidic and give rise to 'late' endosomes. This increasing acidity leads to the dissociation of lysosomal enzymes. Late endosomes also fuse with primary lysosomes (which contain lysosomal hydrolases and bud from the Golgi) to form secondary lysosomes. Secondary lysosomes might remain in the cell and become residual bodies, or be transported to the cell surface, where they fuse with the plasma membrane and exocytose their digested materials.[3]

Lysosomal enzymes are synthesized with an N-terminal sequence of 20-25 aminoacids recognized by signal recognition particle which enable the nascent polypeptide to be transferred across the membrane of endoplasmic reticulum. Signal peptidase removes signal peptide. Preformed oligosaccharides undergo N-glycosylation with asparagine residue. Furthermore sulfatase family members are formed from sulfated mono and polysaccharides, glycolipid and hydroxyl steroids, and are modified in endoplasmic reticulum.

Lysosomal enzymes are synthesized and are glycosylated in the rough endoplasmic reticulum. They are then transferred to the Golgi bodies, where they acquire mannose-6-phosphate (M6P) residues on their high-mannose and hybrid-type oligosaccharide chains. This recognition marker is specific to lysosomal hydrolases and allows these hydrolases to be sorted from other proteins. Upon arrival of golgi the oligo saccharide chain of lysosomal enzymes are further trimmed and modified by the addition of complex sugar residues , sulfate groups and by the formation of M6P recognition marker.[4]

Enzymology of lysosomes: Some important enzymes found within lysosomes include:

- Lipase, which digests lipids
- Amylase, which digests amylose, starch, and maltodextrins
- Proteases, which digest proteins
- Nucleases, which digest nucleic acids
- Phosphoric acid monoesters

The proteolytic capacity of lysosomes comprises a mixture of endo- and exo-peptidases, called cathepsins, which act in concert to degrade proteins to a mixture of amino acids and dipeptides.[5&6] Some cathepsins, for example, G and E, also function outside the lysosome. All of the proteases are active at an acidic pH, although this may not be their pH-optimum. They are synthesized in the form of inactive precursors, preproenzymes, which are transported to the lysosome by the mannose-6-phosphate pathway like other lysosomal hydrolases. Proteases are classified by the catalytic residue in the active site involved in the mechanism of peptide bond cleavage. Cathepsins with a serine (cathepsins A and G), cysteine (B, C, F, H, K, L, O, S, and W) or an aspartic acid (D and E) residue in the active site have been characterized.[6]

Endopeptidases

- Cysteine proteases: cathepsins B, C, H, K, L, O, S, and W
- Aspartyl proteases: cathepsins D and E
- Serine proteases: cathepsin G in azurophil granules of neutrophils

Exopeptidases

- *Carboxypeptidases*: lysosomal carboxypeptidase (cathepsin A or protective protein)—serine protease; cathepsin B

(dipeptidase); cathepsin X, mono- or dipeptidase; lysosomal carboxypeptidase B; prolylcaboxypeptidase; peptidyl dipeptidase B

- *Aminopeptidases:* cathepsin H—true aminopeptidase; dipeptidyl peptidase I (cathepsin C); dipeptidyl peptidase II; tripeptidyl peptidase (TPP-I)

Lysosomal enzymes in various cells: Lysosomes are subcellular organelles which perform many important cellular functions. For example, lysosomes digest foreign material and engulfed viruses and bacteria presenting in phagosomes during the process of phagocytosis. The influx of neutrophils and mononuclear phagocytes into tissues may be seen as the hallmark of inflammation and significantly contributes to both the injury and the subsequent repair seen in the normal tissues.

Lysosomes are found in all eukaryotic cells, but are most numerous in disease-fighting cells, such as leukocytes[7] found that peritoneal macrophages in culture release lysosomal enzymes in response to phagocytic, but the mechanisms that regulate macrophage lysosomal enzyme secretion are not fully understood. Polymorphonuclear leukocytes also release lysosomal enzymes during phagocytosis[7] and the mechanisms that control this secretary process are well documented.

Macrophage lysosomal enzyme release has many similarities to secretion from polymorphonuclear leukocytes and it is tempting to suggest that the processes might be regulated in the same way. Thus, macrophage lysosomal enzyme release is not controlled by the same regulatory mechanisms as the degranulation processes in polymorphonuclear leukocytes, platelets, and mast cells. Lysosomal enzyme release from macrophages is a much slower process than secretion from the other cell types and this may be functionally very important. Prolonged enzyme release from macrophages is consistent with the major role of this cell in chronic inflammation.

In contrast, mast cells, granulocytes and platelets, which contribute primarily to acute inflammation, exhibit rapid degranulation processes. Platelets secrete lysosomal enzymes during the "platelet release reaction" early in clot formation. During the "platelet release reaction" induced by thrombin or collagen, mammalian blood platelets secrete lysosomal enzymes into the surrounding medium.[8&9] Finally, inflammatory substances may leak from cells simply as a result of cell death due to plasma membrane injury . A number of animal, bacterial, and chemical toxins, as well as synthetic detergents may cause such lysis of the outer cell membrane.

FUNCTIONS OF LYSOSOMES[10]

Cellular Digestion: Lysosomal enzymes degrade proteins into dipeptides and carbohydrates into monosaccharides. Sucrose and polysaccharides are not digested and remain in the lysosomal vacuoles.

Autophagy: By the process of autophagy, lysosomes constantly remove cellular components like mitochondria etc. Cytoplasmic organelles become surrounded by smooth endoplasmic reticulum and lysosomes attach with it and discharge their contents into autophagic vacuole and the organelle is digested. Autophagy is a general property of eukaryotic cells.

Exocytosis: Contents of the primary lysosome mat be released into the medium by exocytosis and it occurs during replacement of cartilage by bone during development where osteoclasts release lysosomal enzymes . It can also occur in bone remodeling under influence of parathyroid hormone. Crinophagy refers to the process by which secretary granules produced in excess are removed by lysosomes.

Endocytosis: Lysosomes may fuse with vesicles or vacuoles formed by endocytosis and release their enzymes into it for digestion. The material for digestion may be food (protozoa) or a foreign body like parasite .The products of digestion are absorbed and assimilated leaving undigested which are released outside by exocytosis.

Role in germ cells and fertilization: The acrosome in spermatozoa may be considered as a special lysosome containing protease and hyaluronidase along with acid phosphatase .The lysosome in ova help in digestion of stored food

Role of lysosomes in diseases: Lysosomes are involved in many diseases like rheumatoid arthritis, silicosis, acute inflammatory responses, anorexia, myocardial infarction, different storage diseases etc.

Lysosomal enzymes release

Although a series of studies have indicated that mechanism which account for release of lysosomal enzymes can provoke acute inflammation, may progressed to chronic state also.

Regurgitation during feeding: Human neutrophils release lysosomal hydrolases during phagocytosis. Microtubules were more prominent in phagocytosing than in resting cells, and were observed near primary lysosomes and forming phagosomes. "Regurgitation during feeding" resulted from degranulation of primary lysosomes into newly formed phagosomes which were still open to the extracellular space as well as from the ingestion of additional material directly into already loaded secondary lysosomes.[11]

Phagocytosis: When cells engage in phagocytosis (leukocytes which engulf immune complexes in the synovial fluid of patients with rheumatoid arthritis) they release a portion of their lysosomal hydrolases into the surrounding medium . This effect appears due to extrusion of lysosomal materials from incompletely closed phagosomes open at their external border to tissue space while joined at their internal border with granules discharging acid hydrolases into the vacuole (phagolysosome). Under such circumstances lysosomal enzymes are selectively released to the outside of the cell without necessarily causing cytoplasmic damage.[12] Reverse Endocytosis: It and may be pertinent to the pathogenesis of tissue injury. When leukocytes encounter immune complexes which have been dispersed along a nonphagocytosable surface,there is similar, selective release of lysosomal enzymes directly to the outside of the cell.

Perforation from within: Another mechanism for lysosomal enzyme release followed phagocytosis of crystals was due to "perforation from within" of the lysosomal membrane, rather than lysis by crystals of the plasma membrane. Enzyme release occurs when certain materials gain access to the vacuolar system wherein they interact with, and finally rupture, lysosomal membranes . A wave of membrane damage results with release of cytoplasmic and lysosomal enzymes followed by cell and tissue death.[11]

Regulation of lysosomal proteases

Selective secretion of lysosomal enzymes from neutrophils during acute inflammation. Discharge of lysosomal content is requires extracellular calcium and can be modulated by several different classes of hormones, protease inhibitors such as α2 -macroglobulin and α1-antiprotease, drugs and other agents which results in the provocation of acute inflammation and connective tissue degradation. These antiproteases are present in serum and synovial fluids. They are thought to function by binding to and covering the active sites of proteases. Protease-antiprotease imbalance is probably important in the pathogenesis of emphysema. The most prominent protease inhibitor in human

serum is α1-antitrypsin. It has the highest molar concentration of all inhibitors and is responsible for approximately 90% of the total trypsin-inhibiting activity of normal serum α1-antitrypsin is a glycoprotein with a carbohydrate portion of 12.4% containing galactose, mannose,fucose, acetyl hexosamine, and sialic acid. Its amino acid composition is unremarkable except perhaps for the content of only two cysteine residues[13&14]

CONCLUSION

Concluding, the present study, the lysosomal enzymes are crucial for the degradation of numerous macromolecular substrates and have been involved in many inflammatory responses. Our understanding of the importance of lysosomal cysteine proteases has advanced considerably in recent years. It is now evident that they regulate biological processes such as matrix remodeling and the immune response. Although their exact roles in the pathobiology of various diseases are uncertain, continued research should clarify their roles in various grounds. Accurate knowledge of lysosomal enzyme is essential to expand our current understanding of intracellular proteolysis that plays important role in health and disease.

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