Role and Molecular Mechanisms of Lysosomes and Cathepsins in Neuropathology and Aging: New Insights

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Abstract

Lysosomes are the major catabolic entities that target a large number of biomolecules and pathogens as well. These cytoplasmic organelles play a substantial role in maintaining homeostasis with the aid of a vast assortment of its cathepsins. Cathepsins and its variants are reported to be involved in multiple physiological activities including apoptosis, coagulation, cell proliferation, immunity, and digestion, etc. These cathepsins are responsible for apoptosis leading to neuropathological changes and aging. Among various types of cathepsins, cathepsin B, D and L, are responsible for aging and neurodegenerative disorders, either by activation of microglia or production of inflammosomes. Aging is also attributed to lysosomal storage diseases caused by impairment in lysosomal function and lipofuscin accumulation. So, lysosomes are not only the dumping ground of the cellular waste but also tightly linked to autophagy at the signaling level. This balance has to be strictly controlled by catabolic capacity of the cell, which is accomplished by ubiquination and autophagic machinery to control aging. Furthermore, lysosomes play critical role in life expectancy via a vast variety of signaling pathways and enhanced lysosomal activity that can improve life span. Taken together these considerations, this review provides an insight into the role of cathepsins in various animal models in autophagy and aging. Furthermore, molecular mechanisms underlying the role of lysosomes and altered expression of cathepsins in neurodegenerative changes and cellular longevity has been reported. Thus, improvement or enhancement in lysosomal activity may prove an ideal strategy to extend life span.

Keywords
Aging, Brain, Cathepsins, Healthspan, Life span, Lysosomes, Neurodegeneration, Neurons

Novelty of the Study

Lysosomes are the major catabolic machinery that degrades several biomolecules and pathogens. They do so by a vast assortment of their cathepsins and help in maintaining homeostasis. Cathepsins and their variants are reported to be involved in multiple physiological activities including apoptosis, coagulation, cell proliferation, immunity, and digestion, etc. Here, we have reviewed the role of lysosomes and cathepsins in various nervous system pathologies and aging. Moreover, we have provided an insightful approach that targeting these cathepsins may promise better future therapies to improve not only the life span but also the healthspan.

Introduction

Lysosomes, single membrane-bounded organelles, are characterized as major catabolic entities and have been reported in all types of animal cells except red blood cells (RBCs). There is a long list of substances targeted and degraded by ly-
Lysosomes including pathogens, a variety of biomolecules, surface proteins, old/worn-out organelles, and many other particles. Catabolic function of lysosome is attributed to a variety of acidic hydrolases. Lysosomes play their substantial role in a variety of biological activities like development, apoptosis, waste disposal, plasma membrane repair and maintenance, stress management, nutrient supply, cellular differentiation, and many more to help and maintain cellular homeostasis [1-3]. Discovery of lysosomes was a milestone achievement to get an insight into proteolysis [4]. They have a battery of enzymes and also named as suicide bags because of their involvement in the intracellular degradation of different substances. Lysosomal hydrolases also have a very specific role in protein degradation [5].

Cathepsins are a group of protein-digesting enzymes and are classified into various families i.e. serine, cysteine and aspartyl proteases [6]. Fifteen (15) classes of cathepsins in total have been identified so far [7]. These lysosomal enzymes are highly dynamic in their actions and are involved in multiple physiologic activities i.e. autophagy, apoptotic cell death, blood coagulation, cell proliferation, immunity, and digestion among many more [8-10].

Proteins are continuously being synthesized and degraded in the cell [11]. This is a time saving strategy of the proteins during destruction or alteration when exposed to an unsafe cellular environment. Superficially, the renewal of cellular components seems to be a waste of resources but actually, it is beneficial to the cell because the accumulation of futile components may jeopardize the survival and function of the cell [12]. Besides, protein breakdown is a recycling process as the resulting amino acids are reused [11]. However, the rate of protein degradation varies among cells, under different circumstances and in response to different stimuli. The balance between protein breakdown and protein synthesis is very crucial as it helps the cell to adapt always changing extracellular surroundings by rapidly modifying intracellular proteins. The cell responds to stress routinely by activating its protein degradation systems [12,13]. The role of these proteolytic systems in the well-being of the cell is supported by molecular chaperones. These chaperones determine whether to refold, repair or destroy the proteins. If suitable, they help to repair or refold the proteins, otherwise, proteins are destined to proteolysis (Figure 1). Proteolysis is a fundamental requirement in the elimination of pathogens/invaders and some developmental processes i.e. differentiation, morphogenesis, and embryogenesis [14,15]. There are two key systems for protein breakdown: Rapid non-lysosomal protein degradation system or ubiquitin-proteasome system [16] and the second one is the lysosome-autophagy system [13,16].

Aging and Lysosomes

Aging is characterized by inevitable poor physiological integrity and altered or impaired body activities thus enhance the liability to death. Nine hallmarks of aging include deregulated nutrient sensing, stem cell exhaustion, genomic instability, lost proteostasis, altered intercellular communication, telomere attrition, mitochondrial dysfunction, cellular senescence, and epigenetic alterations [17]. Furthermore, malfunctioned intracellular proteolytic mechanisms arbitraged by the lysosome results in collapsed homeostasis [18]. Cathepsins trigger apoptosis in aging and impaired endosomal-lysosomal neuron system [19]. Among various types of cathepsins, cathepsins B, D, and L are responsible for aging. Previously, injection of leupeptin (cysteine cathepsin inhibitor) or chloroquine (a lysosomotropic drug) into the brain of young rats led to decreased dopamine receptors and accumulation of lipofuscin which are otherwise observed only in aged brain [20,21]. Cathepsin B is a lysosomal cysteine protease and is known to be involved in neuropathological and neurodegenerative disorders [8,22]. Leakage of cathepsin B from the lysosome into the cytosol in microglia is associated with cognitive impairment [23]. Nakanishi, et al. [24] reported that the level of cathepsin B in the brain of all the aged animals except in the striatum have relatively constant activity, where its activity increases with age. Also, a significantly decreased level of cathepsin L has been observed in the brain of aged rats. The presence of a catalytically inactive form of cathepsin L can be suggested from this study, probably because of lysosomal pH alterations as it is highly susceptible to a high pH [24]. Manganese and propagation of lysosome were also observed in the hippocampus upon cathepsins B and L inhibition suggesting that megalenuite may store catabolic organelles. Separation of these megalenuites from paren cells was proposed to result in axotomy. So, the inhibition of cathepsin L may trigger a faster gerontological sequence somewhat resembling aging in cultured slices [25]. Porta, et al. [26] reported a constant level of cathepsin B histochemically in the brain of 14-24 months-old rats [26]. The presence of cathepsin B has been confirmed immunologically in several neurons and astrocytes [27]. Microglia comprises about 20% of the total glial cell population and are distributed in the central nervous system (CNS). Microglia, once activated, are sources of cathepsins and play a key role in neuroinflammation and neurodegenerative diseases in aging [28-30]. In response to Aβ, NALP3 inflammasome-mediated production of IL-1β is because of cathepsin B [31]. Similarly, the expression of another microglia-secreted cathepsin S has been...
E (an aspartic protease) was hardly detected in any brain part. The activity of cathepsin D amplified in aged rats compared to the young rats in all brain tissues, but levels of cathepsin E were found to be increased only in the neostriatum and cerebral cortex [24]. The higher expression of cathepsins D and E and their co-localization with lipofuscin in aged rat's neurons and brain are in complete agreement with a previous study that indicates alterations in the lysosomal proteolytic system, suggesting an altered lipofuscinogenesis and intracellular APP (amyloid precursor protein) metabolism [20,24]. Variation in cathepsin D expression during postnatal development of CNS in the rat is suggestive of a possible role of this important enzyme in myelination [42]. Cathepsin D was found in neurons and glial cells of humans. Its level markedly elevates during neuro-ontogenesis [36]. During the age transition, pronounced alterations were observed in lysosomes of different regions of the rat brain [43]. In 35% of neurons of cerebral cortex age-related changes viz., translocation of cathepsin D from lysosomes to cytosolic granules were observed. However, the pattern of variation of cathepsin B indicates that it regulates brain aging differently. Translocation of cathepsin D from the lysosome to cytosol leads to cell death in the aged brain [44]. Earlier, instability of the lysosome was considered as a reason for the release of cathepsin D [39]. However, the translocation of this enzyme was not due to the changed permeability of the lysosomal membrane. Later on, cathepsin D was anticipated as a potential biomarker of aging [45]. Overexpression and translocation of cathepsin D result in the presence of molecular targets of cathepsins in CNS. Cathepsin D has involved in the breakdown of sever-
al proteins i.e. tubulin and microtubule-associated proteins (MAP-1 & MAP-2) in an age-dependent manner [38]. These alterations suggest that substrate and enzyme specificity is vulnerable during aging [46]. In the cytosol of the hippocampus, tau protein serves as a target of cathepsin D; but requires suppression of cathepsin B. This suppression results in an increased lysosomal pH that ultimately enhance the proteolysis of tau protein. During brain aging, the shift of pH may ignite a series of reactions in the inactivation of cathepsin L that in turn stimulates the expression of cathepsin D resulting in proteolysis of tau [25]. There are several factors that affect the aging (Table 1).

Lysosomes are key players in several cellular processes that control organismal death and apoptosis. Thus, any impairment in lysosomal function may lead to several lysosomal storage diseases (LSDs) [47]. Mutations in any of the genes responsible for hydrolases can lead to LSDs with infants being more susceptible than adults but sometimes adults are also affected by LSDs that result in neurodegeneration [19]. Several organs are affected and undergo tissue degeneration, however, LSDs have distinct effects both in patients and animal models [48]. CNS is most vulnerable that is adversely affected by LSDs with infants being more susceptible than adults but sometimes adults are also affected by LSDs that result in neurodegeneration [19]. Several organs are affected and undergo tissue degeneration, however, LSDs have distinct effects both in patients and animal models [48].

Table 1: Factors affecting different types of aging and their effects.

| Factors affecting aging | Effects | Type of Aging | References |
|------------------------|---------|---------------|------------|
| Cathepsin B, D and L   | Decrease in dopamine receptor and accumulation of lipofuscin | Neurodegeneration | [20-22,36] |
| Cathepsin K, S, V      | Skin aging with structural-functional changes in extracellular matrix | Elastin degeneration | [116] |
| Cathepsin K            | Angiogenesis | Cardiovascular disease | [117] |
| Cathepsin S            | Diurnal variation in strength of neurons | CNS inflammation and aging, post menopausal osteoporosis | [34,118] |
| Cathepsin X            | Regulates brain functions via gamma enolase | Neuroinflammation | [33] |
| Cathepsin C            | Neutrophils recruitment and production of chemokines and cytokines | CNS inflammation and aging | [119] |
| Cathepsin E            | Lipofuscinogenesis and altered APP metabolism | Neurodegeneration | [20,40] |
| NSCs                   | Accumulation of protein aggregates and decrease in lysosomal function | Neurodegeneration | [120] |
| LSDs                   | Accumulation of lysosomal material | Neurodegeneration | [19] |
| Decreased activity of GBA | Elevated level of alpha-synuclein | Parkinson’s disease | [54] |
| Mammalian target of rapamycin complex 1 (mTORC1) kinase complex | Lysosomal biogenesis and autophagy regulation | Control life span in worms | [58] |
| Stored amino acids and metals | Change in intralysosomal pH | Aging | [60-62] |
affected by metals (i.e. Ca\(^{++}\) and Fe\(^{++}\)) and stored substrances (i.e. amino acids), these substances are vital to maintain the coordinated lysosomal expression and regulation (CLEAR) network [58-61].

**Lysosomes and Autophagy Regulation in Aging**

The survival of an organism is governed by its capability to sustain a balance between the production of new stuff and the degradation of old harmful cellular structures. This balance is strictly controlled by catabolic capacity of the cell, which is accomplished by two processes: 1) Ubiquitin/proteasomal degradation pathway, mainly targets cytosolic and endoplasmic reticulum (ER) proteins following their retrograde transport to the cytosol while ubiquitinated mitochondrial proteins are exposed [62,63], 2) Autophagic machinery destroys cytosolic substrates, from single proteins to whole organelles which are delivered to the lysosome for hydrolytic damage. Both pathways control aging [64-67], and also interact with each other [68], but their role in life span control still needs more investigation. Three major subcategories of autophagy are chaperone-mediated autophagy (CMA), macroautophagy, and microautophagy [69]. CMA is a selective protein targeting pathway that directs the substrate translocation to lysosomes during aging [70,71]. Microautophagy involves direct invagination of cytosolic material at the lysosomal membrane [72] which needs further investigations [71]. Macroutaphagy is a recyclable process of lysosomes that maintains cellular homeostasis [73]. In macroautophagy, the target material is engulfed in autophagosomes, transported to the lysosome, where the membrane of autophagosomes fuses with lysosome causing the formation of a single membrane vesicle which is degraded in the lumen [74]. Macroautophagic machinery is exceedingly conserved, from unicellular yeast to mammals [75]. Macroutaphagy is responsible for life span control [56,71,76-78]. The rate of autophagy is decreased in aging [71]. On the contrary, pharmacological and genetic modulations enhance autophagic activity by extending longevity. Thus, aging is controlled by the regulatory genes of all steps of autophagic process viz, 1) Regulation/initiation, 2) Phagophore formation, 3) Cargo loading and degradation [56,78]. Autophagy deficiency has been found to decrease the life span and in contrast, accelerated age-related pathologies [74]. For instance, mutations in any of the two principal initiation complexes of autophagy (ULK1 and Beclin-1) resulted in a reduced life span, premature aging and age-related pathologies [79,80]. Tissue-specific ATG5-KO and ATG7-KO resulted in accelerated aging and age-related problems [49]. These problems include the accumulation of lipofuscin [77], lipid droplets, defective mitochondria [81], and excessive protein oxidation along with neurodegeneration [50,82]. The third step of autophagy can further be divided into three sub-stages: 1) Cargo recognition and loading; 2) Delivery to and fusion with a lysosome; 3) Lysosomal degradation. Any defect in these stages may lead to an abnormal autophagic flux [83] and may result in many neurodegenerative disorders, including Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis (ALS). Furthermore, a mutation in p62, which is a crucial marker for autophagic flux especially in the cargo-recognition machinery which transports substrates to autophagosomes can further enhance autophagy and lead to onset of ALS and Paget’s disease [84-86]. These findings suggest that autophagy is commonly aberrant in neurodegenerative diseases. However, further studies are still required to explore specific autophagic or signaling pathways involved in different types or sub-types of neurodegenerative diseases [87].

**Lysosomal contributions in anti-aging activities:**

Progressive lysosomal dysfunction can lead to aging, and based on this information a question arises that whether any improvement or enhanced lysosomal activity can improve or extend life span or not? A large number of studies carried out in various model organisms have proven this speculation to be right. For instance, an improvement in life span was observed in *S. cerevisiae* upon over-expression of Pep4 (a homolog of cathepsin D) [88]. Similarly, an upregulated level of LIP1-4 (lysosomal acid lipase) has been attributed to an extension in the life span of *C. elegans* [89]; via fatty acid oleoylthanolamide (OEA) production [57]. Furthermore, life span extension via autophagy induction has been observed as a result of overexpression of TFEB homolog in *C. elegans* (HLH-30) [90] as HLH-30 along with MXL-3 (another transcription factor) is responsible for lysosomal lipolysis. Therefore, a mutation in MXL-3 led to an extension of the life span [91]. Overexpression of N-ethyl-maleimide sensitive fusion protein (NSF1) resisted the development of neurodegeneration in *D. melanogaster* perhaps via activation of lysosomal proteases and autophagy induction [92]. Likewise, Akt2 ablation prolongs life span and improves myocardial contractile function with a possible adaptive cardiac remodeling through the sirutin 1 (SIRT1) mediated autophagy regulation in mice [93]. Furthermore, induction of autophagy using rapamycin, resveratrol, nicotinamide derivatives, metformin, urolithin A, or spermidine have been reported in previous studies to delay aging, prolong life span, and improve cardiovascular function in aging [94]. Taking together these findings it can be concluded that increased lysosomal performance may protect organisms from aging-associated pathologies. Similarly, the lysosomal function improves healthspan and life span. This association emerges from the important role of lysosomes observed in autophagy [78]. Life span extension is strictly related to the induction of autophagy and therefore controls aging. Spermidine is a naturally occurring polyamine [95] and its level decreases with age and triggers autophagy. Spermidine treatment in yeast brings about histone H3 hypo-acetylation probably by inhibition of acetyltransferases, which results in loss of autophagy essential gene, ATG7 [96]. Autophagy is induced by spermidine injections, accompanied by inhibition of acetylation of different cytosolic proteins [97]. Resveratrol is a polyphenolic compound present in grapes and red wine and affects stress-related targets, among them, is the Nicotinamide adenine dinucleotide (NAD\(^{+}\)) dependent deacetylase SRT1 [98]. Interestingly, SRT1 stimulation causes the deacetylation of autophagic proteins and their succeeding activation [99]. In *C. elegans*, autophagy activation is necessary for longevity mediated by resveratrol [100]. Certain anti-aging interventions appear due to the combined effect of direct
or indirect repression of target of rapamycin (TOR) signaling [101]. Likewise, rapamycin, a direct mTORC1-inhibitor also act as a strong inducer of autophagy [102], among mTOR-independent pathways, the transient receptor potential (TRP) calcium ion channel TRPML (mucolipin) subfamily is emerging as an important signaling channel to modulate lysosomal bio-
genesis and autophagy [73]. Similarly, activated acetyltans-
ferase MEC-17 promotes autophagy by stimulating cellular
microtubule transport machinery [103]. On the other hand, 
biguanide metformin secondarily inhibits TOR activity by in-
hibiting oxidative phosphorylation, which brings about a rise 
in AMP/ATP ratio and activation of AMPK [104]. In the mean-
time, metformin can up-regulate REDD1 and hinder Ras-re-
lated GTP binding (Rag) GTPases, and together they promote 
repression of TOR [105]. The contribution of lysosomes in 
these mediations presumably traverses pass their degrada-
tive potential. mTORC1-docking is essential for the activity 
of lysosomes and lysosomes control their mTORC1-docking on 
their surface by a luminal cargo of amino acids, essential for 
its movement [106]. Some novel anti-aging interventions may 
go to the bleeding edge. Dietary supplementation of lysosom-
ally produced OEA advances life span in worms [57] and can 
subsequently be a potential contender for the dietary anti-ag-
ing approach. An exceptionally successful behavioral attitude 
in contrast to aging is exercise, which not only increases life 
span [107] but also has universal health benefits [108]. Exer-
cise has been displayed to begin autophagy flux in the muscle 
[109]. Interestingly, autophagy induced by exercise entails the release of lysosomal Ca\textsuperscript{2+} from lysosomal calcium channel 
mucolipin 1 and succeeding activation of calcineurin in which 
sequence stimulates nuclear translocation of TFEB [61]. Most 
of the anti-aging involvements converge in lysosome at differ-
ent levels, highlighting lysosomal function as a vital molecular 
hub for controlling health span and life span.

Some other molecular mechanisms which are central to 
autophagy regulation and impact life span are transcriptional 
and epigenetic regulation of autophagy genes. Recent studies 
have shown that tissue-specific induction of autophagy can 
also result in non-cell autonomous extension of organismal 
life span [110]. Although, the mechanism of non-cell auto-
nomous autophagic regulation is currently unclear, inter-tissue 
communication of stress responses such as the heat shock 
response and unfolded protein responses in the endoplas-
mic reticulum (UPR\textsuperscript{ER}) and mitochondrial (UPR\textsuperscript{mt}) have been 
demonstrated [111]. These organelle-specific and intracellu-
lar proteostatic mechanisms may potentially be involved in 
depicting autophagic status between tissues to regulate aging. 
Also, autophagy proteins can also possess some autoph-
agy independent functions [112] such as extracellular protein 
secretion [113], that may mediate inter-tissue integration of nutrient signalling, metabolism, and gene regulation to mod-
ulate proteostasis. As certain temporal and circadian consid-
erations are now being integrated in aging studies [114], the 
underlying mechanisms that affect autophagy and proteostas-
is and lead to neurodegeneration are bound to be clarified and 
new exploitable mechanisms are likely to be uncovered.

Conclusion

Taking into account the above literature it can be con-
cluded that lysosomes are major catabolic organelles that not 
only help in the breakdown of various substances rather they 
are the major players in various nervous system pathologies 
and aging via cathepsins. Hence, targeting these cathepsins 
may promise better future therapies to improve not only the 
life span but also the healthspan.

Conflict of Interest Statement

None declared.

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Authors Contributions

MBK, NF, MHA, RM, ZA and ZS, AA, TS collected the data 
and performed literature review. MK, NF, MHA and RM write 
the draft and provided professional guidelines. MBK and NS 
conceived the idea, approved the final manuscript and super-
vised the whole project.

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