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·Review·

Chaperone-mediated autophagy: roles in neuroprotection

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Chaperone-mediated autophagy (CMA), one of the main pathways of lysosomal proteolysis, is characterized by the selective targeting and direct translocation into the lysosomal lumen of substrate proteins containing a targeting motif biochemically related to the pentapeptide KFERQ. Along with the other two lysosomal pathways, macro- and micro-autophagy, CMA is essential for maintaining cellular homeostasis and survival by selectively degrading misfolded, oxidized, or damaged cytosolic proteins. CMA plays an important role in pathologies such as cancer, kidney disorders, and neurodegenerative diseases. Neurons are post-mitotic and highly susceptible to dysfunction of cellular quality-control systems. Maintaining a balance between protein synthesis and degradation is critical for neuronal functions and homeostasis. Recent studies have revealed several new mechanisms by which CMA protects neurons through regulating factors critical for their viability and homeostasis. In the current review, we summarize recent advances in the understanding of the regulation and physiology of CMA with a specific focus on its possible roles in neuroprotection.

Keywords: chaperone-mediated autophagy; cellular homeostasis; neuroprotection; neuronal death; neurodegenerative disease

Introduction

Maintaining the balance between protein synthesis and degradation contributes to cellular homeostasis[1-3]. The ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP) are major systems present in almost all cell types to mediate the degradation of intracellular proteins into their constitutive amino-acids[4, 5]. The UPS is a multi-subunit protease complex that degrades proteins tagged with one or more covalently-bound ubiquitin molecules, and most proteasome substrates are proteins with a short half-life[6, 7].

In contrast to the UPS, the ALP is mainly responsible for the degradation of long-lived proteins and organelles. On the basis of the mechanism used for delivery of intracellular cargoes to lysosomes, autophagy can be divided into three types: macroautophagy (MA), microautophagy, and chaperone-mediated autophagy (CMA)[8, 9]. Both CMA and MA have been identified in mammals as processes important for damage and diseases of the central nervous system[10]. MA is a bulk degradation system that involves the formation of a double-membrane structure (autophagosome) that sequesters damaged organelles and proteins. The autophagosome acquires the hydrolytic enzymes necessary to degrade its cargo by fusing with lysosomes[11]. Microautophagy traps nonspecific cytoplasm inside vesicles *via* direct invagination of the lysosomal membrane. These vesicles "pinch off" into the lumen and are degraded by lysosomal hydrolases[12].

CMA is the third type of autophagy, and has so far been found only in mammalian cells[13, 14]. One of its intrinsic features is the selective targeting and direct translocation into the lysosomal lumen of substrate proteins containing a targeting motif related to the pentapeptide KFERQ[15, 16]. This selectivity allows for the removal of misfolded, oxidized, or damaged cytosolic proteins under physiological or

pathological conditions without perturbing normally-functioning forms of the same proteins[17-19]. CMA potentially regulates multiple cellular processes by the selective removal of inhibitors of transcription, enzymes, and cell-maintenance proteins[17, 20].

In this review, we first briefly summarize the main mechanisms of CMA under physiological conditions and then discuss its roles in neuroprotection and the therapeutic potential of targeting this pathway for the treatment of brain diseases.

Molecular Mechanisms of CMA

CMA is a complex process that can be divided into four distinct steps: (1) binding of substrates to the chaperone protein Hsc70 and targeting to lysosomes; (2) binding of substrates to the lysosomal receptor LAMP2A (lysosome-associated membrane protein type 2A) and unfolding; (3) substrate translocation into lysosomes; and (4) substrate degradation by hydrolytic enzymes in the lysosomal lumen[21].

During the first step, CMA substrates containing the pentapeptide motif KFERQ bind to the constitutive chaperone Hsc 70 in the cytosol[22-24]. Many other chaperones are also involved in this process, such as Hsp40, Hsp90, and Hip[25-27]. Although amino-acid sequence analysis shows that almost 30% of cytosolic proteins contain a KFERQ-like sequence, only a few have been experimentally confirmed to be degraded through this process[28]. Some characteristics associated with this motif are notable: (1) the CMA motif is based on the charge of the amino-acids; (2) post-translational modifications such as phosphorylation and acetylation can change the amino-acid charge and enable them to acquire a more effective motif recognizable by the CMA process[24, 29]; and (3) alternatively, a string of imperfect and overlapping motifs can also serve to mediate the CMA process[30]. Thus, containing a functioning KFERQ-like motif is the first requirement for a protein to be considered as a possible CMA substrate. The 'gold standard' to validate a protein as a CMA substrate is the lysosomal binding and uptake assay.

During the second step, the Hsc70-co-chaperone/substrate complex translates to the lysosomal membrane and binds to the cytosolic tail of LAMP2A[31]. The levels and conformational status of LAMP2A are critical for the CMA process, and this is a rate-limiting step for the process. LAMP2A exists as a monomer at the lysosomal membrane and forms a multimeric complex in association with other proteins[26]. CMA substrates first bind to monomeric LAMP2A present at the lysosomal membrane and this interaction drives LAMP2A multimerization to produce a 700-kDa complex required for the translocation of substrate into the lysosome. Once substrate proteins translate into the lysosomal lumen, lysosomal Hsc70 (lys-Hsc70) promotes disassembly of the LAMP2A multimerization complex to enable monomeric LAMP2A to bind to other substrates[26]. A portion of the LAMP2A may be transported into the lysosomal lumen and degraded by cathepsin A[32]. Many factors participate in regulating the assembly/disassembly of the LAMP2A multimerization complex, such as changes in the fluidity of the lysosomal membrane or protein and lipid composition[33]. GFAP and EF1-alpha have been shown to regulate the assembly/disassembly of the LAMP2A multimerization complex[34].

Translocation of substrate proteins into the lysosomal lumen requires lys-Hsc70[25]. The mechanisms by which lys-Hsc70 contributes to translocation remain to be elucidated. It may function by pulling substrate proteins or may immobilize them to prevent their return to the cytosol. The stability of lysosomal Hsc70 is regulated by lysosomal pH and small increases in pH are sufficient to exacerbate its degradation[35]. However, the mechanisms by which Hsc70 translates to lysosome remain largely unknown.

Although the molecular mechanisms by which CMA is modulated are poorly understood, CMA activity is closely associated with the levels of LAMP2A at the lysosomal membrane, and modulation of the LAMP2A content by cells can rapidly change the activity of this pathway[31]. The synthesis/degradation of LAMP2A and its redistribution from the lysosomal lumen to the lysosomal membrane all contribute to its levels at the membrane. In addition, lipid microdomains and cathepsin A play an important role in regulating the levels of this protein[32]. Previous studies have shown that lys-Hsc70 is a limiting factor in the modulation of CMA[35, 36]. Without lys-Hsc70, substrate protein cannot be translocated into the lysosomal lumen, and the level of lys-Hsc70 increases gradually with upregulation of CMA activity.

Physiological Role of CMA

As one of the cellular quality-control systems, CMA was first proposed to participate in amino-acid recycling[37]. When cells or animals are exposed to serum deprivation or prolonged starvation, CMA is maximally activated due in part to increased LAMP2A transcription, decreased LAMP2A clearance, or increased levels of lys-Hsc70. Although removal of serum from cell cultures or prolonged starvation in animals can activate both MA and CMA, the kinetics of these reactions appears to be different. MA is maximally activated shortly after these treatments (~4–6 h) and persists for a short period of time. However, CMA is activated later (~8–10 h) and persists much longer[37]. The selectivity of CMA may promote cellular survival under serum deprivation or prolonged starvation by maintaining essential proteins and removing non-essential proteins, such as glycolytic enzymes and inhibitors of transcription factors containing a KFERQ-like motif in their amino-acid sequences[38].

In addition, CMA contributes to the selective removal of aberrant or damaged proteins in order to maintain cellular homeostasis. Under oxidative stress, up-regulation of CMA promotes the degradation of oxidatively-damaged proteins[39]. In support of this idea, CMA increases under oxidative stress or exposure to toxic compounds[40]. Inhibition of CMA significantly exacerbates the accumulation of oxidatively-damaged proteins and decreases cell viability[40]. Furthermore, CMA can specifically remove the damaged subunits of cytosolic protein complexes[41]. Recent studies have shown that hypoxia induces CMA, and up-regulation of CMA effectively protects cells from hypoxia-induced cell death[42]. Although the mechanisms remain poorly understood, CMA may directly target hypoxia-inducible factor 1[43]. Recent studies have shown that CMA regulates tubular cell growth by modulating the degradation of the transcription factor Pax2[44]. Furthermore, CMA is involved in the immune response. Previous studies showed that only MA and UPS participate in processing antigens. However, recent studies have revealed that CMA is involved in antigen processing and presentation. The levels of autoantigen presentation are closely related to CMA activity[45-47].

As the two major proteolytic systems mediating the degradation of intracellular proteins[48, 49], the ALP and the UPS are not isolated and independent but tightly coordinated. CMA may affect the UPS and the other two autophagic pathways, and the UPS and the other two autophagic pathways can also modulate CMA activity. When MA and the UPS are reduced, CMA is usually activated[50]. Conversely, reducing CMA contributes to remarkable up-regulation of MA[19].

CMA and Neuroprotection

Because neurons are postmitotic, they are especially sensitive to homeostatic changes. CMA plays an important role in maintaining cellular homeostasis. Recent studies have shown that the key components of CMA, LAMP2A and Hsc70, are robustly expressed in the CNS[51, 52]; CMA is involved in the regulation of neuronal survival[30]; and CMA dysfunction has been linked to the pathogenic processes of several human disorders[21].

Parkinson's Disease (PD)

PD is the second most common degenerative disease, characterized by the specific loss of dopaminergic neurons in the substantia nigra pars compacta[53]. Although the etiologies of PD remain elusive, protein dyshomeostasis is the critical mechanism responsible for the neuronal death and may be involved in the pathogenesis. Analysis of postmortem brain tissue from PD patients shows that the level of LAMP2A in the substantia nigra is lower than in controls[52]. Cuervo *et al.* reported a link between CMA and the protein α-synuclein, which is the key component of Lewy bodies and whose mutation and level changes are involved in the pathogenesis of PD[54]. They showed that the α-synuclein amino-acid sequence contains a KFERQ-like CMA-targeting motif and confirmed it as a CMA substrate. They found that mutant forms of α-synuclein (A53T and A30P), which cause familial PD, are defective in their uptake by lysosomes due to their tight binding to LAMP2A and cannot be efficiently degraded. Although the study showed how mutation of α-synuclein may contribute to the dysfunction of CMA, it did not identify a direct mechanism by which CMA dysfunction may lead to neuronal death.

We recently showed that CMA directly targets for removal of non-functional myocyte enhancer factor 2D (MEF2D), a factor critical for the survival of dopaminergic neurons. This is critical for maintaining the homeostasis of MEF2D under basal conditions[30, 55]. Overexpression of

wild-type or disease-causing mutant α-synuclein in cells leads to an inhibition of its degradation by CMA. The levels of both MEF2D and α-synuclein are higher in the neuronal cytoplasm in the brains of PD patients than in controls[30, 55]. Thus, dysregulation of MEF2D homeostasis by CMA is a feature of PD. We tested the function of MEF2D that had accumulated in the cytoplasm due to defective CMA and found that the accumulated MEF2D had a much lower DNA-binding activity than controls[30]. Since increased MEF2D in the nucleus attenuates α-synuclein-induced cellular toxicity, our findings established a direct relationship between CMA and the nuclear survival machinery, indicating that its disruption may underlie the toxic effects of both wild-type and mutated α-synuclein.

Since increased oxidative stress has been proposed to play a critical role in the pathogenesis of PD, we further investigated its role in the CMA-mediated maintenance of MEF2D homeostasis. Our results showed that oxidative stress leads to direct oxidative modification of MEF2D and a significant decrease in its level[40]. This decrease is in part due to the accelerated removal of oxidized MEF2D by CMA. Consistently, the levels of oxidized MEF2D are much higher in the postmortem PD brain than in controls, consistent with the notion that reduced CMA in PD leads to the accumulation of damaged MEF2D, disrupting its homeostasis and function.

A recent investigation of leucine-rich repeat kinase 2 (LRRK2), mutation of which is linked to PD, showed that it is a CMA substrate[56]. LRRK2 G2019S, the most common mutant form, is poorly degraded by this pathway. Lysosomal binding of both wild-type and several pathogenic mutant LRRK2 proteins is enhanced in the presence of other CMA substrates, which may interfere with the organization of the CMA translocation complex, resulting in defective CMA. Similarly, ubiquitin C-terminal hydrolase L1 (UCH-L1), mutation of which is linked to familial PD, is degraded by CMA[57, 58]. It has been shown that the PD-related mutant UCH-L1 I93M binds much more tightly to Hsc70/hsp90 and LAMP2A present at the lysosomal membrane than the wild-type protein. Therefore, it may block CMA *via* mechanisms similar to those proposed for α-synuclein or LRRK2.

Alzheimer's Disease (AD)

AD is the most common neurodegenerative disease and is closely associated with aging. CMA gradually decreases with physiological aging. Previous studies have shown that dyshomeostases of intracellular proteins are critical factors in the pathogenesis of AD, one of which is abnormal tau metabolism[59]. Tau pathology in AD is characterized by its aggregation and cleavage[60]. How tau protein is degraded remains controversial. Wang *et al*. showed that CMA contributes to tau fragmentation into pro-aggregating forms and to the clearance of tau aggregates[61]. Tau_{RD}DK280 and its F1 fragment interact with the cytosolic chaperone Hsc70 and with the CMA receptor LAMP2A. Unlike typical CMA substrate proteins, these forms of tau are not translocated into lysosomes by CMA. Instead, they aggregate on the outer membrane of lysosomes, leading to the disruption of lysosomal membrane integrity and blockade of other CMA substrates.

Huntington's Disease (HD)

HD is caused by polyQ repeat expansion of huntingtin (Htt)[62]. The accumulation of aggregated mutant Htt protein in the affected neurons is its hallmark[63]. Clarifying the mechanisms that influence the cellular degradation of Htt may help to understand the pathology of the disease and identify a cure. However, the mechanisms by which Htt is degraded remain largely unknown. Several studies have demonstrated that MA regulates the degradation of Htt and an increase in MA activity may protect neurons[64]. Recent studies have shown that CMA may also be involved in Htt degradation[65, 66]. When post-translationally modified by phosphorylation/ubiquitination/SUMOylation and acetylation, Htt may bind to Hsc70 and LAMP2A with higher affinity[24]. Consistent with the involvement of CMA in HD, the activity of this pathway appears to increase in mouse models of HD.

Therapeutic Perspectives

Dyshomeostasis of proteins may be the cause of many diseases. A decrease in CMA plays an important role in the dyshomeostasis of various proteins. Therefore, restoration of CMA activity may be a strategy for treating many diseases, especially neurodegenerative diseases. Combinations of different types of approaches, including genetic methods and CMA-modulating drugs, have succeeded in slowing down the neurodegeneration in mouse models of HD and PD. It has been reported that

retinoic acid receptor alpha (RARα) negatively regulates CMA activity, and inhibition of RARα with synthetic derivatives of all-trans retinoic acid can specifically activate CMA. Activation of CMA by RARα can protect cells from oxidative stress and proteotoxicity[67].

Conclusions

CMA is an important proteolytic pathway characterized by selectivity and direct translocation of substrate proteins across the lysosomal membrane. It is critical for maintaining cellular homeostasis and for many different aspects of cell physiology, especially in the central nervous system. The roles of CMA in the physiological functions of neurons and in the pathogenesis of neurodegenerative diseases are largely unknown. Further investigation of its functions should help understand the pathogenic mechanisms underlying these diseases. Since a decrease in CMA is associated with many neurodegenerative diseases of aging, increasing CMA by various means should be explored as a treatment strategy.

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