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Chaperone-mediated autophagy: dedicated savior and unfortunate victim in the neurodegeneration arena

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Abstract

The importance of the cellular quality control systems in the maintenance of neuronal homeostasis and in the defense against neurodegeneration is well recognized. Chaperones and proteolytic systems, main components of these cellular surveillance mechanisms, are key in the fight against the proteotoxicity that is often associated with severe neurodegenerative diseases. However, in recent years, a new theme has emerged that suggests that components of the protein quality control pathways are often targets of the toxic effects of pathogenic proteins and that their failure to function properly contributes to pathogenesis and disease progression. In this mini-review, we describe this dual role as “savior” and “victim” in the context of neurodegeneration for chaperone-mediated autophagy, a cellular pathway involved in the selective degradation of cytosolic proteins in lysosomes.

Keywords

aging; autophagy; chaperones; lysosomes; neurodegeneration; proteotoxicity

Proteotoxicity and autophagy: a two-sided coin

Intracellular accumulation of aberrant proteins is a feature shared by the group of human disorders known as protein-conformational diseases. The best known among these diseases are neurodegenerative conditions in which abnormal proteins accumulate in the form of inclusions in the affected neurons. It is well accepted that neurons utilize systems present in all cells to fight against the toxic effects of these aberrant proteins.

A network of chaperones and proteolytic systems are at the forefront of the cellular response to protect against proteotoxicity [1, 2]. Chaperones recognize undesirable protein modifications or conformational defects and bind to abnormal proteins to prevent their nonspecific interactions with other components of the functional proteome. In addition, chaperones assist in the repair of proteins and attempt to return them to a stable conformational state. When this fails, they target aberrant proteins to the cellular proteolytic machinery for degradation. The contribution of the two major cellular proteolytic systems, the ubiquitin proteasome and lysosomes, to the cellular defense against proteotoxicity has

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been extensively reported and in fact, the therapeutic value of enhancing the activity of these pathways in different neurodegenerative settings is being explored [2]. However, the applicability of these types of interventions may have some limitations depending on the status of the proteolytic systems in the disease.

Growing evidence supports that pathogenic proteins can interfere with the normal function of the ubiquitin-proteasome pathway and with the different pathways for delivery of cytosolic components to lysosomes for degradation through autophagy. A reduction in the activity of these systems further increases cellular proteotoxicity and limits the potential for success of interventions that rely on fully functional proteasomal and lysosomal degradation. Recent reviews have described changes in the ubiquitin/proteasome pathway and macroautophagy, the best characterized type of autophagy, in the context of neurodegeneration and readers are encouraged to consult that literature [3, 4]. In this mini-review, we focus on a type of autophagy known as chaperone-mediated autophagy (CMA) that is distinguished from other autophagic variants by the fact that substrate proteins are delivered to the lysosomal lumen through a membrane translocation complex rather than in vesicles [5]. As described below, CMA is an efficient pathway for removing abnormal and damaged proteins, however, the physical properties of the translocation system and the unique characteristics of the surrounding lysosomal membrane make CMA a frequent target of the toxic effects of pathogenic proteins in neurodegeneration.

Chaperone-mediated autophagy, a vesicle-free entry to the lysosomes

CMA is a distinct autophagic pathway present in all mammalian cells in which cytosolic proteins are delivered and degraded inside lysosomes in a highly selective manner [5]. This selectivity is achieved by the heat shock cognate protein of 70 KDa (hsc70), that identifies and delivers individual protein substrates one-by-one to the surface of lysosomes (Fig. 1) [6]. A pentapeptide motif in the amino acid sequence of the substrate protein enables its recognition and subsequent targeting to the lysosomal compartment by hsc70 [7]. Once the protein reaches the lysosomal membrane, it binds to a single-spanning membrane protein, the lysosome associated membrane protein type 2A, or LAMP-2A [8]. Binding to substrates drives LAMP-2A to oligomerize into a multimeric translocation complex that allows proteins to cross the membrane and enter the lysosomal lumen (Fig. 1) [9]. Once inside, resident hydrolases catabolize proteins into small peptides and amino acids which can be recycled back to the cellular cytosol for other uses.

Since LAMP-2A serves as the CMA receptor as well as the translocation complex, its levels are directly correlated with CMA activity. Interestingly, levels of LAMP-2A at the lysosomal membrane can be regulated at the transcriptional level as well as post-translationally [10]. Transcriptional upregulation occurs in certain proteotoxic conditions, such as oxidative stress, and leads to higher rates of degradation through CMA [11]. In other types of stress conditions such as nutrient deprivation, increases in LAMP-2A and subsequently in CMA are attained by enhancing LAMP-2A stability in the lysosomal membrane [10]. Several regulatory molecules have been identified to play a role in modulating the amount of LAMP-2A at lysosomes and thus influencing CMA activity. For example, intraluminal chaperones such as Hsp90 have been shown to preserve the stability

of LAMP-2A while it undergoes conformational changes into the multimeric translocation complex [9]. Other interacting proteins present on the surface of lysosomes such as GFAP and EF1 α modify the dynamics of the LAMP-2A assembly and disassembly process [12]. Different environmental stressors have also been shown to interfere with CMA function through changes in the dynamics of the CMA receptor at the lysosomal membrane. For instance, an increase in dietary fats leads to changes in the lipid composition of the lysosomal membrane that render LAMP-2A unstable and consequently disrupt the normal function of CMA [13]. Similarly, age is inversely correlated with CMA activity: older organisms have lower levels of LAMP-2A and diminished capacity to perform CMA [14]. This age-related functional decline contributes to the accumulation of abnormal and dysfunctional proteins and may also exacerbate disease progression of age-related pathologies.

Chaperone-mediated autophagy in the fight against proteotoxicity

The first physiologic stressor found to activate CMA was prolonged starvation. Absence of nutrients for more than 10 hours results in a gradual increase in CMA activity with a peak activation at 48h post nutrient deprivation that is sustained for as long as the nutritional challenge persists [15]. Selective breakdown of superfluous proteins through CMA during starvation may contribute amino acids required for protein synthesis and facilitate changes in the proteome required for the adaptation of the cell to these new conditions.

CMA is also activated in circumstances associated with cytosolic protein damage, such as oxidative stress. Exposure of cells to oxidants and pro-oxidants leads to a rapid activation of CMA through transcriptional upregulation of LAMP-2A [11]. Proteins bearing the CMA targeting motif that become damaged during oxidative stress are readily identified by hsc70 and delivered to lysosomes for degradation (Fig. 1). Interestingly, uptake of these oxidized proteins is faster than for their unmodified counterparts, suggesting that some level of unfolding prior to lysosomal targeting may occur in the cytosol [11]. Despite the presence of other systems for clearance of oxidized proteins, such as the proteasome and macroautophagy, experimental blockage of CMA has been shown to lead to the accumulation of oxidized cytosolic proteins in different cellular models [16]. These findings support the existence of a pool of proteins that when they become oxidized, their CMA degradation is favored over their removal through other pathways. In addition, the type and source of the oxidative stress may also determine the preference for one proteolytic system or another [17].

The importance of CMA in the degradation of oxidized proteins has been also demonstrated *in vivo* in the context of physiological aging [18]. CMA activity has been shown to decrease with age in most organs in rodents and in primary skin fibroblasts and peripheral leukocytes of healthy human subjects [14, 19]. This decrease is due to the reduced stability of LAMP-2A at the lysosomal membrane with age [20, 13]. Restoration of normal levels of the CMA receptor in old animals through genetic manipulation markedly reduces the intracellular accumulation of oxidized proteins characteristic of aging tissues [18], thus supporting the importance of CMA in the cellular defense against oxidative damage. Growing evidence supports that activation of CMA is also a common response in the central

nervous system to the oxidative stress associated with different chronic neurodegenerative disorders. An increase in CMA markers has been observed in response to 6-hydroxydopamine-induced lesions in the nigrastratial pathway [21]. Likewise, levels of LAMP-2A have been shown to increase in response to seizures and status epilepticus, conditions associated with excessive production of reactive oxygen species [22].

CMA is also part of the cellular response to other stressors such as hypoxia, where CMA upregulation enhances cell survival (Fig. 1) [23]. The fact that the hypoxia-inducible factor 1 (HIF-1 α) has recently been identified as a CMA substrate places this autophagic pathway at the center of the regulation of the cellular response to hypoxia [24]. Upregulation of CMA components has been also described in response to the activation of pro-apoptotic program in a common form of rod-cone dystrophy, indicating that CMA is part of the pro-survival response in retinal cells [25]. In fact, the response to stress in cone photoreceptors seems to rely in large part on CMA activity, which explains the increased sensitivity of these cells to different stressors when CMA is compromised [26].

The role of CMA in neuronal survival goes beyond the mere elimination of the fraction of the proteome damaged by the stressor. In fact, in many instances, CMA directly contributes to the selective turnover of specific proteins that govern the stress-response. For example, CMA regulates the function of essential components of the neuronal survival machinery, such as the transcription factor myocyte enhancer factor 2D, by facilitating the removal of the inactive form of this factor from the cytoplasm (Fig. 1) [27].

Tight connections between CMA and neurodegeneration originated from the realization that many of the proteins related to the pathogenesis of common neurodegenerative disorders contain a CMA-targeting motif in their amino acid sequence (Fig. 1). Alpha-synuclein, a main component of the protein inclusions detected in almost all forms of Parkinson's diseases (PD), was the first of these proteins validated as a *bona fide* CMA substrate [28]. Degradation of α -synuclein through CMA was later confirmed by other groups in neuronal cultures [29] and *in vivo* models where midbrain neurons were shown to respond to genetic and chemically-induced increases in wild type α -synuclein levels by upregulating CMA [30]. Conversely, genetic enhancement of CMA has recently been shown to be protective against the dopaminergic neuronal degeneration induced by adenoviral-mediated increases in levels of wild type α -synuclein [31]. CMA degradation has also been described for the wild-type forms of other PD-related proteins such as UCH-L1 [32] and more recently the leucine-rich repeat kinase type 2 protein LRRK2 [33]. The growing list of neurodegeneration-related CMA substrates goes beyond PD and includes proteins associated with the pathogenesis of Alzheimer's disease such as tau [34], the regulator of calcineurin 1 [35], and proteins associated with spinocerebellar ataxia such as ataxin-7 [36].

In the case of Huntington's disease, although CMA does not significantly contribute to the degradation of full length wild-type huntingtin, cleavage products of this protein are turned over by this lysosomal pathway [37]. For example, phosphorylation and acetylation of the N-terminal fragment encoded by exon 1 of huntingtin drives its degradation through CMA. In fact, genetic upregulation of CMA in brain slices over-expressing this toxic huntingtin variant has a positive effect [38]. The interplay of huntingtin and CMA is particularly

interesting as this is so far the only neurodegenerative disorder for which efficient degradation by CMA of the mutant form of the protein has been demonstrated both in neuronal cultures and in mouse models *in vivo* [39]. Interestingly, artificial enhancement of CMA targeting of mutant huntingtin with adaptor molecules effectively reduces levels of this toxic protein and improves neuronal pathology in HD mouse models [40]. This type of intervention may have therapeutic potential as CMA is constitutively upregulated in HD-affected neurons, likely in response to the blockage of other degradative pathways [39]. However, the window of therapeutic opportunity could be narrow since an abnormally accelerated decline in CMA has been observed in HD neurons with age [39].

Functional failure of CMA in neurodegenerative diseases

Malfunction of cellular quality control mechanisms has been proposed to underlie the basis of disease progression in a growing number of neurodegenerative disorders. Reduced CMA activity has also been described in some of these conditions and often the pathogenic proteins are the ones to blame for CMA failure.

Alpha-synuclein was the first protein for which a toxic effect on CMA was described [28]. In contrast to the efficient degradation of wild-type α -synuclein by CMA, forms of this protein bearing pathogenic mutations in their sequence are poorly removed by this form of selective lysosome degradation. This ineffective degradation does not result from problems with the targeting of the mutant variants to the lysosomal compartment but instead from their faulty translocation across the lysosomal membrane. In fact, mutant forms of α -synuclein remain tightly bound to the lysosomal receptor which prevents the degradation of any other common CMA substrate in this compartment [28]. Compromise of CMA was also observed in the case of the wild-type form of the protein when present in abnormally high levels inside cells [28, 41] and even at low levels if the wild-type protein has been subjected to specific undesired posttranslational modifications such as those mediated by dopamine reaction [42]. A similar inefficient CMA degradation and blockage of this pathway has been shown for other PD-related proteins such as mutant forms for UCH-L1 [32].

Although multiple factors are likely to contribute to defective degradation of pathogenic proteins and to the blockage of CMA in PD, recent studies on the interplay of the PD-related protein LRRK2 with CMA have shed light on the precise mechanism behind CMA failure (Fig. 1). As described before, LRRK2 has been identified as a *bona fide* CMA substrate. Pathogenic mutants of this protein, or even the wild-type form of LRRK2 when present at high levels, disrupt the assembly of the CMA translocation complex at the lysosomal membrane, compromising its own degradation and that of other substrates of this pathway, including α -synuclein [33]. The LRRK2-mediated inability of LAMP-2A to organize into complexes, leaves higher amounts of monomeric forms of LAMP-2A at the lysosomal membrane, explaining the increased lysosomal association of other CMA substrates such as α -synuclein observed under these conditions [33]. Even with wild type α -synuclein, the presence of mutant LRRK2 is sufficient to promote toxic oligomerization of α -synuclein at the lysosomal membrane due to the compromise in lysosomal translocation. The presence of these oligomeric forms of α -synuclein stuck at the lysosomal membrane further compromises CMA activity [33]. Interestingly, artificial mutations that prevent delivery of

α -synuclein to the lysosomal membrane improve cell survival, partially because it no longer impedes CMA function [29]. Similarly, chemical [43] and genetic [31] upregulation of CMA reduces cellular toxicity associated with α -synuclein.

Neuronal cells respond to CMA toxicity mediated by pathogenic proteins by upregulating this autophagic pathway [30, 33]. However, studies in iPS cells from PD patient have revealed that the initial upregulation of CMA is followed by a marked decrease in CMA activity as the disease progresses [33]. Late downregulation of this pathway is also supported by the reduced expression of L2A and hsc70 identified in peripheral leucocytes in idiopathic forms of PD [44] and in the substantia nigra pars compacta of PD brains [45]. Although the mechanisms behind this downregulation of CMA require further study, microRNAs reported to increase in PD experimentally reduce expression of LAMP-2A and hsc70 [46] and thus, could contribute to the observed decline in CMA associated with disease progression. However, it is also possible that in specific PD settings, a primary defect in the transcriptional regulation of CMA components may contribute to disease exacerbation. For example, a sequence variation in the promoter region of LAMP-2 that decreases its transcriptional activity has been identified in a PD patient [47].

Blockage of CMA has also been observed in the context of pathogenic proteins related to other neurodegenerative disorders. Pathogenic mutant variants of Tau are less amenable to CMA degradation and interfere with CMA function [34]. In this case, the aberrant proteins do not block formation of the translocation complex, but instead their passage through this complex is interrupted before the full protein reaches the lysosomal lumen (Fig. 1). This blunted translocation results in the generation of amyloidogenic fragments of Tau through partial cleavage of the part of the protein that reaches the lysosomal lumen [34]. Oligomerization of these fragments at the lysosomal surface further contributes to blockage of CMA. Mutant γ PKC, the protein implicated in the pathogenesis of spinocerebellar ataxia type 14, has also been shown recently to reduce CMA activity in cultured cells although the mechanism has yet to be elucidated [48].

Besides the direct toxic effects of pathogenic proteins on CMA, it is also possible that primary defects in the molecular regulators and effectors of this pathway may underlie the basis of some neurodegenerative disorders. For example, mutations in the transient receptor potential mucolipin-1 (TRPML1), a protein located in lysosomes, have been shown to result in neuronal cell death but how it induces apoptosis is unknown. The fact that chaperones involved in CMA have recently been shown to interact with this lysosomal membrane protein and that levels of LAMP-2A are reduced in cells expressing mutant variants of TRPML1 opens the interesting possibility that neuronal death in these patients may be a result of defective CMA [49].

Concluding remarks

CMA is an important component of the cellular response to proteotoxic stressors. The ability of this pathway to selectively eliminate altered proteins and to modify the cellular proteome to adapt to the stress conditions support the potential therapeutic value of interventions that enhance CMA activity. The number of compounds capable of activating CMA is still rather

limited but the promising results observed through genetic manipulations of this pathway in the context of aging and neurodegeneration provide rational support for further development of chemical modulators of CMA. However, therapeutic interventions will have to take into account the toxic effect that pathogenic proteins can exert on CMA. Higher success is anticipated for early interventions that are initiated before CMA toxicity occurs, whereas at later stages it may be necessary to consider treatments that combine pharmacological activation of CMA with compounds that prevent abnormal interactions between pathogenic proteins and essential CMA components.

Abbreviations

CMA	chaperone-mediated autophagy
hsc70	heat shock cognate protein of 70kDa
LAMP-2A	Lysosome-associated membrane protein type 2A

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Figure 1. Chaperone-mediated autophagy and Neurodegeneration

CMA is responsible for the selective degradation of cytosolic proteins that are delivered to lysosomes by the chaperone hsc70. Once at the lysosomal membrane, binding of the substrate to the cytosolic tail of LAMP-2A induces its multimerization into a translocation complex that assists in the internalization of the substrate into the lysosomal lumen for degradation. **A.** Examples of mechanisms by which CMA contributes to the defense against neuronal proteotoxicity. **B.** Examples of mechanisms for CMA compromise in neurodegenerative disorders.