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REVIEW

Malfunctioning of Chaperone-Mediated Autophagy in Parkinson's Disease: Feats, Constraints, and Flaws of Modulators

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Abstract

Homeostatic regulation of class II programmed cell death/autophagy for the degradation and elimination of substandard organelles and defective proteins is decisive for the survival of dopaminergic neurons. Chaperone-mediated autophagy (CMA), one of the most highly dedicated self-sacrificing events, is accountable for the partial elimination of redundant soluble cytoplasmic proteins in Parkinson's disease (PD). CMA is characterized by the selective delivery of superfluous protein containing lysine-phenylalanine-glutamate-arginine-glutamine (KFERQ)/KFERQ-like motif to the lysosome through molecular chaperones, such as heat shock cognate-70 (Hsc-70). KFERQ/KFERQ-like motif present in the poor quality cytoplasmic substrate protein and Hsc-70 complex is recognized by a janitor protein, which is referred to as the lysosome-associated membrane protein-2A (LAMP-2A). This protein is known to facilitate an entry of substrate-chaperone complex in the lumen for hydrolytic cleavage of substrate and elimination of end-products. Impaired CMA is repeatedly blamed for an accumulation of surplus soluble proteins. However, it is still an enigma if CMA is a bonus or curse for PD. Case-control studies and cellular and animal models have deciphered the contribution of impaired CMA in PD. Current article updates the role of CMA in toxicant models and recapitulates the evidences that have highlighted a link between impaired CMA and PD. Although PD is an irreversible happening and CMA is a dual edging phenomenon, it is anticipated that fine-tuning of the latter encounters the former to a certain extent. Besides, the truth, embellishment, and propaganda regarding the issue are also emphasized in the final segment of the article.

Keywords Parkinson's disease · Chaperone-mediated autophagy · Toxicant models · Parkinsonism

Introduction

Selective degeneration of the nigrostriatal dopaminergic neurons, reduced dopamine content in the striatum, formation of Lewy bodies and onset of behavioral, motor, phenotypic, psychiatric, sensory, and cognitive anomalies have been found to be associated with Parkinson's disease (PD) (Smith et al. 2003; Singhal et al. 2012). Lewy bodies are basically the intra-cytoplasmic inclusions, composed of atypical α-synuclein and a few other non-functional cytoplasmic proteins (Cuervo and Wong 2014). Owing to that, sporadic/idiopathic PD is also referred to as α-synucleinopathy or proteinopathy disorder (Sala et al., 2016a). Autophagy, on the other hand, is an essential auto-scarifying cellular event accountable for the degradation and elimination of redundant soluble proteins and defective sub-cellular organelles through hydrolytic enzymes in the acidic environment of the lysosomes (Mishra et al. 2015). This key eukaryotic phenomenon is also referred to as class II programmed cell death since it helps in retaining the homeostatic cellular health and mitochondrial quality control. Autophagy is involved in the clearance of highly toxic proteins and damaged organelles. It is known to regulate protein dynamics through recycling. Furthermore, autophagy is found to delay the normal aging process (Cuervo and Wong 2014; Cai et al. 2015). Chaperone-mediated autophagy (CMA) is recognized as a highly selective and specialized form of autophagy. CMA plays a decisive role in the removal of futile soluble proteins from dopaminergic neurons of the

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nigrostriatal tissue. Therefore, it has been implicated in PD pathogenesis and treatment outcomes (Xilouri et al. 2016; Yang et al. 2016; Sala et al. 2016a). Besides, wild-type α-synuclein is also found to be primarily degraded by CMA in the neurons (Vogiatzi et al. 2008; Cuervo and Wong 2014).

Intra-cytoplasmic aggregate formation, mitochondrial dysfunction, excessive free radical production, reduced endogenous antioxidants, and defective clearance of poor quality organelles and proteins through autophagy and ubiquitin-proteasome system are found to be linked with PD pathogenesis. Additionally, several other known and elusive pathways are also known to contribute to PD (Yang et al. 2016; Mishra et al. 2015; Haynes et al. 2004). CMA and macroautophagy are accountable for maintaining the steady state of the cellular proteins and functions that usually control bioenergetics, mitochondrial excellence and protein quality (Yang et al. 2016; Sala et al. 2016, 2016a). A connecting link among CMA, mitochondrial quality control, and bioenergetics is therefore inevitable. An existence of a dynamic link is supported by the fact that CMA participates in the elimination of myocyte-specific enhancer factor 2D (MEF2D), which is not only a neuronal survival factor but also a mitochondrial function regulator (Yang et al. 2016). Besides, redundant ubiquitin C-terminal hydrolase L1 (UCH-L1), leucine-rich repeat kinase-2 (LRRK2), and several other mitochondrial and cytoplasmic proteins are also shown to alter CMA and thereby PD pathogenesis, either directly or indirectly (Cuervo and Wong 2014; Sala et al. 2016a). Impaired CMA is anticipated in increasing the disease severity since it exerts harmful effects on dopaminergic neurons due to an abnormal protein accumulation that eventually leads to motor, psychiatric, sensory, and other secondary symptoms.

Natural/synthetic agents that regulate the level of a CMA marker to some extent are shown to possess protective effects. Strategies used to modulate CMA markers, such as regulation of lysosome-associated membrane protein-2A (LAMP-2A) expression, are shown to counteract α-synuclein toxicity and PD-like symptoms (Zhu et al. 2014; Su et al. 2016; Murphy et al. 2015; Xilouri et al. 2016; Wang et al. 2017; Kiffin et al. 2004; Xilouri et al. 2013; Moors et al. 2017; Patel and Cuervo 2015). It is rather complicated to utterly detach macroautophagy with CMA owing to an existence of an active crosstalk between the two. Likewise, an identical aspect is also noted between the modifiers of the two. Despite all, the selectivity of CMA is maintained and is found to be important in the regulation of cellular response to stress (Massey et al. 2006). This observation is supported by the fact that CMA modifiers/modulators regulate α-synuclein aggregation, cell death, oxidative stress, and mitochondrial dysfunction, the key events typically compromised in PD and toxicant models (Moors et al. 2017; Gong et al. 2018; Anguiano et al. 2013). Contrary, dose-dependent side effect of modulators is also seen that dampens their subsequent clinical usage (Moors et al. 2017).

Current article compiles the information available in the scientific literature on CMA and PD/Parkinsonism. Information gathered from environmental/toxicant and genetic/hereditary models along with post-mortem human brains is brought together and discussed. Moreover, some of the potential modulators and their impact on CMA markers are also deciphered. Translational value of modulators has been the major concern for researchers and clinicians. While the fine-tuning of CMA in a few models of Parkinsonism is booming, the same is not found to be successful in many other models. Moreover, fine-tuning of autophagy is not yet tested in the clinical scenario (Moors et al. 2017; Finn et al. 2005; Anguiano et al. 2013). Reality, propaganda and myth related to such issues are also summarized at the end of the article.

CMA Is a Framework of Chaperones and Membrane Proteins for the Removal of Redundant Proteins by the Specialized Proteins

In general, a protein in association with another protein or a bunch of proteins performs a function to maintain the homeostatic operation in the cells of an organism. However, an exception is always there, which is pertinent to an enzyme and its protein substrate where one protein (enzyme) runs after the other (substrate). CMA is a classical instance of such a natural protein framework where a redundant soluble cytoplasmic protein is degraded and eliminated via the lysosome through hydrolytic enzymes, which are also proteinaceous in nature. While the majority of unwanted proteins are degraded and eliminated by the ubiquitin-proteasome system following polyubiquitination, a few are degraded and eliminated by the lysosome-dependent autophagy after mono- or polyubiquitination. Regardless of the fact that CMA merely eliminates misfolded and oxidized cytoplasmic proteins in part (Cai et al. 2015), malfunctioning could lead to the formation and accumulation of protein aggregates.

Several cytosolic and lysosomal chaperones, membrane bound proteins, receptors, and proteinaceous substrates have been identified and shown to contribute to CMA (Table 1). Cytoplasmic substrate proteins containing lysine-phenylalanine-glutamate-arginine-glutamine (KFERQ)/KFERQ-like motif are directly presented to the lysosome, and the process is facilitated by the molecular chaperones and lysosomal proteins (Mishra et al. 2015; Cai et al. 2015). Molecular chaperones recognize, transport, and send the targeted substrate proteins to the lysosome (Cuervo et al. 1994). An approximately 70-kDa cytoplasmic chaperone protein, referred to as heat shock cognate-70 (Hsc-70), is known to identify the pentapeptide KFERQ/KFERQ-like motif present in the substrate (Mishra et al. 2015; Agarraberes and Dice 2001). CMA is assisted not only by Hsc-70 but also by a

Table 1 Major proteins associated or cleared off by CMA and their underlying functions

Proteins	Role	Aberration	References
Hsc-70	A carrier protein for α-synuclein and other substrate proteins Binds to KFERQ/KFERQ-like motif of the substrates Participates in α-synuclein fibrils fragmentation and depolymerization	Abnormal functioning/structural change leads to an accumulation of substrate proteins since that inhibits the complex formation with substrate and further translocation	Mishra et al. (2015); Sala et al. (2016); Cuervo et al. (2004)
Hip	This protein participates in the complex formation between the chaperones (Hsc-70/Hsp-40) and substrates Assists in the degradation of unfolded/misfolded proteins	Atypical performance owing to any reasons leads to an accumulation of the substrate proteins in the endoplasmic reticulum	Haynes et al. (2004); Roodveldt et al. (2009)
Hsc-40	Induces ATPase activity and facilitates Hsc-70 and Hip binding	Any changes in the structure or function inhibit CMA and thus facilitate an accumulation of redundant proteins	Majeski and Dice (2004)
LAMP-2A	A specific lysosomal gate-keeper that acts as a receptor for the substrate and Hsc-70 complex Recognizes KFERQ/KFERQ-like motif of the complex and facilitates its selective transport to the lysosomal lumen for degradation and elimination of substrate protein	Any functional abnormality owing to structural changes alters an overall competence of CMA	Cuervo and Wong (2014); Mishra et al. (2015); Cuervo et al. (2004)
Cathepsins	A group of proteases involved in the cleavage of LAMP variants	Abnormal functioning leads to an altered degradation and redistribution of LAMP-2A	Cai et al. (2015); Cuervo et al. (2003)
Glucocerebrosidase	Plays a role in the metabolism of glycolipids and α-synuclein transport for CMA and regulates the function of lysosome	Mutation leading to an abnormal enzyme activity increases α-synuclein accumulation Aberrant enzyme alters the normal functioning of the lysosome thereby CMA	Ambrosi et al. (2015); Richter et al. (2014); Mcneill et al. (2014)
α-Synuclein	A major substrate protein for CMA in PD A sequence similar to KFERQ but not completely alike (KFERQ-like motif) is present in this protein	Any abnormality in this protein alters its accumulation in the nigrostriatal and adjacent brain tissues	Mishra et al. (2015)
UCH-L1	Hydrolyzes small C-terminal adducts of ubiquitin to generate ubiquitin monomer Presence of a catalytic triad (3 amino acids at three positions) is responsible for its activity	Changes in the structure of the gene encoding the protein could increase/reduce PD risk owing to an alteration in the hydrolytic activity	Cuervo and Wong (2014); Mishra et al. (2015)
LRRK2	Mainly a cytoplasmic protein also found to be associated with the mitochondrial membrane	Any change in the function of the protein owing to mutations could lead to its accumulation as it is a known substrate for CMA	Cuervo and Wong (2014); Mishra et al. (2015)
MEF2D	A neuronal survival factor and mitochondrial function regulator	Any change in the function leads to neuronal impairment and mitochondrial dysfunction Gets accumulated as it is a recognized substrate for CMA	Yang et al. (2009)

number of other molecular chaperones, such as Hsc-40, an activator of adenosine triphosphatase activity of Hsc-70 and Hsp-70-interacting protein (Hip) (Majeski and Dice 2004; Kiffin et al. 2004). KFERQ/KFERQ-like motif of substrate-Hsp-70 complex is subsequently identified by the LAMP-2A. It is one of the key molecules regulating CMA owing to its ability to transport substrate proteins to the lysosomal lumen (Mishra et al. 2015). Release of the protein substrate is stimulated by another protein, typically known as B cell lymphoma-2-associated athanogene 1 protein (BAG1) (Agarraberes and Dice 2001; Kiffin et al. 2004; Kermer et al. 2015). Moreover, the role of lysosomal hydrolases and membrane proteins has also been found to be decisive. An acidic environment in the lysosome facilitates the degradation of substrate proteins owing to precise action of hydrolytic enzymes and subsequent elimination of degraded end-

products. Lysosomal membrane proteins are required not only for the transportation of substrates and elimination of the degraded proteins but also for maintaining the acidification (Eskelinen et al. 2003; Saftig and Klumperman 2009). Several CMA substrates, such as α-synuclein, UCH-L1, LRRK2, and MEF2D, have been identified and tabulated in the article (Table 1). Any changes in the function or solubility of a substrate protein owing to single nucleotide polymorphism leading to an abnormal accumulation of the same or other substrate proteins further approve the role of the former substrate protein in CMA regulation (Saftig and Klumperman 2009; Kabuta et al. 2008).

In general, CMA is a key event for the removal of unwanted soluble proteins from eukaryotic cells through hydrolytic proteins. This self-eating phenomenon is directed by multiple chaperones, receptors, and membrane proteins and is eventually scripted by the lysosome. Therefore, it can be appropriately narrated that CMA is the cellular clearance machinery created by the selected proteins, assisted by the unique proteins for the degradation and removal of non-functional soluble proteins through hydrolytic proteins.

Is CMA Really Important in PD or Parkinsonism?

Like all eukaryotic cells, dopaminergic neurons degrade and remove most of the aberrant proteins through macroautophagy. Contrary to this, a few redundant cytoplasmic proteins are partially or significantly degraded and eliminated by CMA. While the role of CMA is widely reported, its precise contribution in PD pathogenesis and treatment outcomes is still a matter of debate. Despite that, many clues are deduced from the scientific studies supporting the role of CMA in PD. For example, aging reduces the expression of LAMP-2A, a key molecule involved in CMA and CMA-dependent degradation. It is corroborated by the observation that the expression of LAMP-2A declines with the age (Massey et al. 2006). This observation is relevant to PD since it is an aging related disorder. Moreover, the reduction in the level of LAMP-2A is found to induce Parkinsonism in experimental animals. If LAMP-2A is silenced, abnormal accrual of redundant proteins, inhibition of CMA, and formation of autophagosome are inevitable to happen (Xilouri et al. 2016). Reduction in the level of specific CMA markers further supports its active involvement in the etiology of PD (Alvarez-Erviti et al. 2010; Klaver et al. 2018; Murphy et al. 2014; Murphy et al. 2015).

Single nucleotide polymorphism/point mutation in any PARK gene leading to altered translated protein product is found to be associated with hereditary PD (Klein and Westenberger 2012). However, the role of PARK genes/proteins has been realized in all forms of PD including, toxicant-induced Parkinsonism and idiopathic PD (Klein and Westenberger 2012). Investigations employing knockout, knockdown, and toxicants models along with the post-mortem brains have also supported the perception (Cuervo and Wong 2014). For example, PARK7 deficiency increases α-synuclein accumulation and aggregation while over-expression is known to attenuate the same. Conversely, α-synuclein over-expression elevates LAMP-2A while PARK7 (DJ-1) deficiency reduces LAMP-2A along with Hsc-70 (Xu et al. 2017). Similarly, single nucleotide polymorphism in a PARK gene leading to an abnormal accumulation or defective clearance of an accumulated protein product further supports the role of CMA in PD. Literature on the neurobiology of PD shows that more than 18 PARK genes are involved in disease pathogenesis along with a few non-PARK genes (Klein and Westenberger 2012). Polymorphism in any of such genes along with the genes directly associated with CMA is expected to modify PD risk and outcome of anti-PD drugs. Interestingly, only a few genes are found to be actively involved in CMA.

CMA is found to be deviant in the nigrostriatal dopaminergic neurons of Parkinsonian brain (Alvarez-Erviti et al. 2010) owing to multiple reasons. Categorically, the functional genetic variation in PARK and non-PARK genes is a cause of concern. Improper binding of the substrate with molecular chaperone is also found to be an important causative factor. Hsp-70, an integral component of CMA, enters the lysosome thus allowing the substrate to enter the acidic medium of the lysosomal lumen (Roodveldt et al. 2009). Another explanation could be a chemical modification in the substrate that alters its binding ability to a key CMA molecule or its own elimination efficiency. For example, dopamine-modified α-synuclein is found to inhibit CMA and thereby stops the progress of its own degradation and elimination (Martinez-Vicente et al. 2008). Even if effective binding occurs, the complex is not precisely recognized by LAMP-2A in a few cases. Besides, irregular LAMP-2A expression, its altered interaction with substrate-Hsc-70 complex, and defective translocation of complex in the lumen are also known to affect the competence of CMA network. Variant forms of CMA substrates, such as α-synuclein or LRRK2, are shown to interact with Hsc-70 and transported to the lysosomal membrane but unable to go through the lumen due to improper translocation (Kabuta et al. 2008; Orenstein et al. 2013; Cuervo et al. 2004). In addition to specific variants mentioned above, many other variants of PARK and non-PARK genes are known (Klein and Westenberger 2012). However, the effect of all such variants on CMA is not yet studied. Moreover, a variant substrate is also found to alter the clearance and transport of other normal/variant substrate proteins. For example, LRRK2 is found to exacerbate α-synuclein translocation and its clearance through CMA (Cuervo and Wong 2014). Besides, normal UCH-L1 is found to interact with Hsc-70/90 as well as LAMP-2A; its I93M variant is shown to increase the

interaction and stops α-synuclein degradation by CMA (Kabuta et al. 2008). All such, probabilities are widely reported and nicely reviewed in detail elsewhere (Cuervo and Wong 2014). While it is not yet studied, the functional single nucleotide polymorphism in non-PARK genes that include β-synuclein, γ-synuclein, leucine-rich repeat kinase 1, ataxins, synphilin 1, microtubule associated proteins, lysosomal receptors, and molecular chaperones could also be linked with impaired CMA since such genes directly or indirectly regulate α-synuclein expression, neurotransmitter release, and neuronal functions. Such probabilities and important experimental observations have shown the importance of CMA in the degradation and elimination of redundant proteins in PD.

Evidence from Sporadic PD

Since PD is a central nervous system syndrome, human studies are quite a few owing to less availability of the post-mortem brains and associated technical and ethical issues. Despite it, a few studies have been conducted on the post-mortem brains that have indicated the involvement of selected CMA proteins. The level of Hsc-70 and LAMP-2A is found to be reduced in the post-mortem brain of PD patients (Alvarez-Erviti et al. 2010). Similar to the reduced LAMP-2A expression in the substantia nigra, LAMP-2 concentration is found to be attenuated in the cerebrospinal fluid of female patients with or without LRRK2 mutations (Klaver et al. 2018). Changes in the level of a CMA marker in the patients as compared with controls directly demonstrate the role of compromised CMA in PD. Moreover, the involvement of impaired CMA in sporadic PD is also evident from the reduced glucocerebrosidase content and abnormal α-synuclein accumulation (Table 2). Early selective PD-associated changes could be due to redistribution of cellular membrane proteins leading to a persistent reduction in the lysosomal function in disease prone areas of the brain (Murphy et al. 2014). Similarly, the selective loss of LAMP-2A, augmented α-synuclein, reduced Hsc-70, and accrual of cytosolic CMA substrates have also highlighted the role of defective CMA in PD. Association of the selective reduction in LAMP-2A and increased α-synuclein levels suggest that impairment of CMA-mediated protein degradation occurs prior to considerable α-synuclein accumulation in PD (Murphy et al. 2015).

Evidence from Parkinsonian Models

Chronic and multi-factorial nature, lack of knowledge about the unambiguous contributory factors, elusive mechanism of disease pathogenesis, and lack of timely diagnosis and permanent therapy most likely make PD as one of the most highly indefinable diseases (Yadav et al. 2012). Rodents are naturally devoid of the symptomatic features of PD; cardinal features can be induced employing a toxicant either alone or in combination with other chemical agent. On that aspect, a few rodents, lower organisms, primates, primary neurons, and cell lines are found to respond to selected environmental toxicants. Moreover, over-expression or downregulation of characteristic PARK genes is also used to develop genetic models in the mentioned cells/organisms. Similarly, over-expression or knockout for CMA proteins is used to understand if CMA is implicated in animal or cellular models (Park et al. 2012; Dong et al. 2005). Toxicant and genetic models are consistently employed to decipher the disease mechanism and its link with CMA. Since implication of CMA in PD is realized in the last decade, only limited reports are available from rodent, cellular and genetic models similar to the post-mortem brains.

Table 2 Status of CMA proteins in sporadic PD/Parkinsonian models

Sporadic/PD models	CMA proteins	Level/status	References
Sporadic PD	Hsc-70 LAMP-2A	Reduced Reduced	Alvarez-Erviti et al. (2010); Murphy et al. (2015)
MPTP model	α-Synuclein	Increased	Kowall et al. (2000)
	LRRK2	Increased	Liu et al. (2016)
	BAG1	Reduced	Kermer et al. (2015)
6-OHDA model	LAMP-2A	Increased	Wang et al. (2017)
	Hsc-90	Increased	Marin and Aguilar (2011)
Rotenone	α-Synuclein MEF2D	Increased Increased	Sala et al. (2013)
	Hsc-70	Decreased	Sala et al. (2016)
Paraquat	LAMP-2A Hsc-90	Increased Increased	Kiffin et al. (2004)
	Hsc-70	Increased	
	α-Synuclein	Increased	Mak et al. (2010)

MPTP

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces the disease features in rodents, primates, neuronal cell lines, and lower organisms for understanding the molecular basis of PD and treatment outcomes (Yadav et al. 2012). Exposure to MPTP modulates the level of CMA marker protein LAMP-2A and increases an accumulation of redundant α-synuclein (Zhu et al. 2014; Su et al. 2016). While sensitivity to MPTP is increased in Hsc-70 knockout mouse, overexpression of Hsc-70 is linked with reduced sensitivity and decreased dopaminergic neuronal loss (Park et al. 2012; Dong et al. 2005). Moreover, elevated level of functional molecular chaperones makes more competent complex with substrate protein for presentation to the lysosome and subsequent clearance. Such observations directly indicate that MPTP impairs CMA. The same is indirectly deciphered from studies conducted to investigate the biochemical and molecular aspects of MPTP-induced Parkinsonism. For example, MPTP is shown to upregulate wild type LRRK2 expression while mutant LRRK2 increases its sensitivity for neurodegeneration (Liu et al. 2016; Wang et al. 2016). Moreover, MEF2D is inhibited by cyclin dependent kinase 5, which in turn accelerates dopaminergic neurodegeneration (Smith et al. 2003). Since the active form of MEF2D is required for normal functioning of dopaminergic neurons, any changes in its level could modify the survival of tyrosine hydroxylase positive neurons. MPTP reduces the level of BAG1 protein that directly regulates accumulation of α-synuclein and other substrate proteins (Kermer et al. 2015). BAG1 is known to accelerate the foldase activity of molecular chaperones and degradation of chaperone-associated proteins. Accumulation of substrate proteins is guarded by specific enzymes that indirectly control MPTP-induced Parkinsonism. For instance, MPTP toxicity is inversely proportional to glucocerebrosidase activity but alteration in enzymatic activity is not associated with increased α-synuclein accumulation (Noelker et al. 2015). Such indirect reports on MPTP-induced Parkinsonism support the relevance of CMA in disease pathogenesis.

6-OHDA

6-Hydroxydopamine (6-OHDA) rodent model is one of the oldest and established models used for understanding the role of oxidative stress in PD. 6-OHDA model minimizes the use of animals since control and exposed tissues can be obtained from the opposite hemispheres of the same brain (Yadav et al. 2012). It is shown to increase the level of Hsp-70 molecular chaperone, Bip, which is located in the lumen of endoplasmic reticulum, without causing any changes in the expression of Hsc-90. Moreover, the level of Hsc-90 is also augmented after 6-OHDA exposure (Ebrahimi-Fakhari et al. 2013; Zhang et al. 2017; Marin and Aguilar 2011; Li et al. 2017). 6-OHDA reduces the stability of F-box protein 7β (FBw7β) that binds to Hsc-70 and regulates CMA. Such studies have shown the involvement of 6-OHDA in the over-expression of molecular chaperones, which bring forth the clearance of redundant proteins and increase an accrual of aggregated proteins in dopaminergic neurons (Wang et al. 2017). However, overexpression of chaperones is not the only mechanism regulating the CMA. Appropriate binding with the substrates and proper delivery and transport to the lumen is shown to be equally important (Cuervo and Wong 2014). 6-OHDA also increases the level of LAMP-2A that causes an excessive degradation of substrate proteins, such as Fbw7β (Wang et al. 2017). Furthermore, 6-OHDA oxidizes and induces an accumulation of MEF2D, which is generally cleared off when LAMP-2A gets increased (Sala et al. 2016a). Activation of CMA related proteins after 6-OHDA exposure confirms that it is aberrant in Parkinsonism.

Rotenone

Rotenone model mimics a few key features of sporadic PD in experimental rodents (Yadav et al. 2012). Like MPTP and 6-OHDA, rotenone also induces an accumulation of CMA substrates, such as α-synuclein and MEF2D (Mader et al. 2012; Sala et al. 2013; Wang and Mao 2014). While rotenone increases α-synuclein and MEF2D biosynthesis, it is not found to control their clearance through CMA. Rotenone does not alter Hsc-70 but increases LAMP-2A mRNA level in SH-SY5Y cells (Sala et al. 2013). Contrary, it is shown to downregulate Hsc-70 mRNA and protein levels in human neuroblastoma cells in another study (Sala et al. 2016). Silencing of Hsp-70 gene was found to upregulate α-synuclein expression without any change in cell viability, which demonstrates that rotenone-induced changes are mediated by Hsc-70 (Sala et al. 2016). Although rotenone alters the expression of a few specific proteins, its role in CMA requires further clues.

Paraquat

Paraquat (an herbicide) either alone or in combination with maneb (a fungicide) induces Parkinsonism in experimental rodents (Yadav et al. 2012; Patel et al. 2006). However, combined exposure rather alone is often preferred to induce a few PD-like symptoms in animals. Paraquat increases the level of LAMP-2A and CMA substrate, glyceraldehyde 3-phosphate dehydrogenase. Paraquat also increases Hsc-90 and Hsc-70 without producing any changes in the expression of BAG 1, Hsp-40, and Hip proteins (Kiffin et al. 2004). Silencing of LAMP-2 is found to increase the cellular mortality in the mouse fibroblast cells after paraquat exposure (Massey et al.

2006). The level and lysosomal clearance of α-synuclein are also found to be augmented in paraquat-exposed mice (Mak et al. 2010). Despite it, paraquat model provides noteworthy observations; studies are insufficient to make a definite conclusion. However, maneb and paraquat combined model is probably not yet used for this purpose.

Pesticide- and Metal-Based Newer Models

In addition to paraquat and rotenone, several pesticides and metals are shown to induce PD-like features in experimental animals (Mishra et al. 2015; Yadav et al. 2012). The role of autophagy in such models has not yet been studied. Moreover, these models per se are at the developmental stage (Mishra et al. 2017). Nonetheless, the role of macroautophagy has recently been shown in cypermethrin-induced Parkinsonism but its link with CMA needs to be deciphered (Mishra et al. 2017).

Other Models/CMA-Associated Protein Knockout/Knockdown Studies

Genetic models are based on the over-expression of specific PARK genes that follow an autosomal (dominant/recessive) pattern of inheritance. Dual models are developed by the amalgamation of over-expression of a PARK gene and a Parkinsonian toxicant (Yadav et al. 2012; Singhal et al. 2012). CMA-based studies are mainly performed in dual (toxicant and genetic) models or in conditions wherein the selected autophagy protein is over-expressed/knocked-down/knocked-out in place of PARK gene per se. Most of the findings reflect the applicability of results for a genetic or dual model of PD. It is known that wild-type α-synuclein is degraded partly by CMA; aberrant α-synuclein acts as CMA inhibitor (Xu et al. 2017; Xilouri et al. 2013). On the other hand, LAMP-2A over-expression is associated with increased CMA and reduced α-synuclein turnover. It is also shown to provide protection from adenovirus-induced wild-type α-synuclein toxicity (Xilouri et al. 2013). Wild-type alpha-synuclein is selectively translocated for degradation by CMA. Despite interacting to LAMP-2A, functional mutants block their own uptake and degradation along with degradation of other substrates (Cuervo et al. 2004). A system, which consists of mutant α-synuclein lacking KFERQ-like motif and RNA interference directed to LAMP-2A, has shown that CMA inhibition leads to an accumulation of soluble and detergent-insoluble α-synuclein entities (Vogiatzi et al. 2008). Moreover, MEF2D interacts with Hsc-70 and gets degraded by CMA. Wild-type α-synuclein and PD-associated mutants are found to reduce the binding of MEF2D with Hsc-70 (Yang et al. 2009). Similarly, LRRK2 is commonly degraded by CMA but its pathogenic variant, G2019S, is poorly degraded. The lysosomal binding of wild-type and pathogenic variant is enhanced in the presence of other CMA substrates leading to malfunctioning of CMA (Orenstein et al. 2013). UCH-L1 also interacts with LAMP-2A, Hsc-70, and Hsp-90, and such interaction is markedly enhanced independent of monoubiquitin binding tendency of UCH-L1 I93M variant. I93M variant-induced inhibition of CMA is found to increase α-synuclein accumulation (Kabuta et al. 2008). The basic mechanism of CMA and major steps which are shown to be affected in the rodents/cellular models are summarized in Fig. 1.

CMA Modulators

Equilibrium between the synthesis and degradation of proteins is responsible for the regulation of neuronal homeostasis (Cai et al. 2015). Although compromised CMA induces an accumulation of redundant proteins, increased CMA promotes neuronal survival (Xilouri and Stefanis 2015). Amelioration is anticipated if endogenous molecules and exogenous chemical agents offer protection from disease progression through a reduction in the accrual of redundant proteins. Chemical agents that alter CMA indicators or network either lessen or boost the CMA (Finn et al. 2005; Anguiano et al. 2013). Most of the effective CMA modulators target the lysosomal receptors, surface proteins, and molecular chaperones (Moors et al. 2017). While genetic over-expression of LAMP-2A activates, knocking down the same reduce the CMA (Patel and Cuervo 2015). It is believed that LAMP-2A knockdown or knockout may help in understanding the CMA modulators better. In the same way, other proteins that regulate the process can be modulated to alter the CMA.

Modulators that reduce the level of CMA marker proteins may not be too useful in rescuing from PD since such agents reduce the clearance of aggregated and soluble protein substrates (Zhang et al. 2014). An endogenous molecule, humanin, is shown to stimulate CMA since this mitochondria-associated macromolecule is found to augment the substrate binding and delivery to the lysosome (Gong et al. 2018). Protein synthesis inhibitors, such as anisomycin and cycloheximide along with p38 mitogen-activated protein kinase (p38MAPK) blockers, are found to inhibit CMA (Finn et al. 2005). Common macroautophagy inhibitors, such as 3-methyladenine, wortmannin, colcemide, vinblastine, and LY294002, are not found to produce any effect on CMA (Finn et al. 2005). It is seen that some of the CMA inhibitors increase macroautophagy but rarely clear off the defective organelles and proteins. Retinoic acid receptor-α signaling is reported to inhibit CMA and stimulate macroautophagy. Several trans-retinoic acid derivatives, such as guanidine retinoids 1, 2, and 7, have been synthesized and are found to encounter CMA inhibition (Anguiano et al. 2013). Owing to

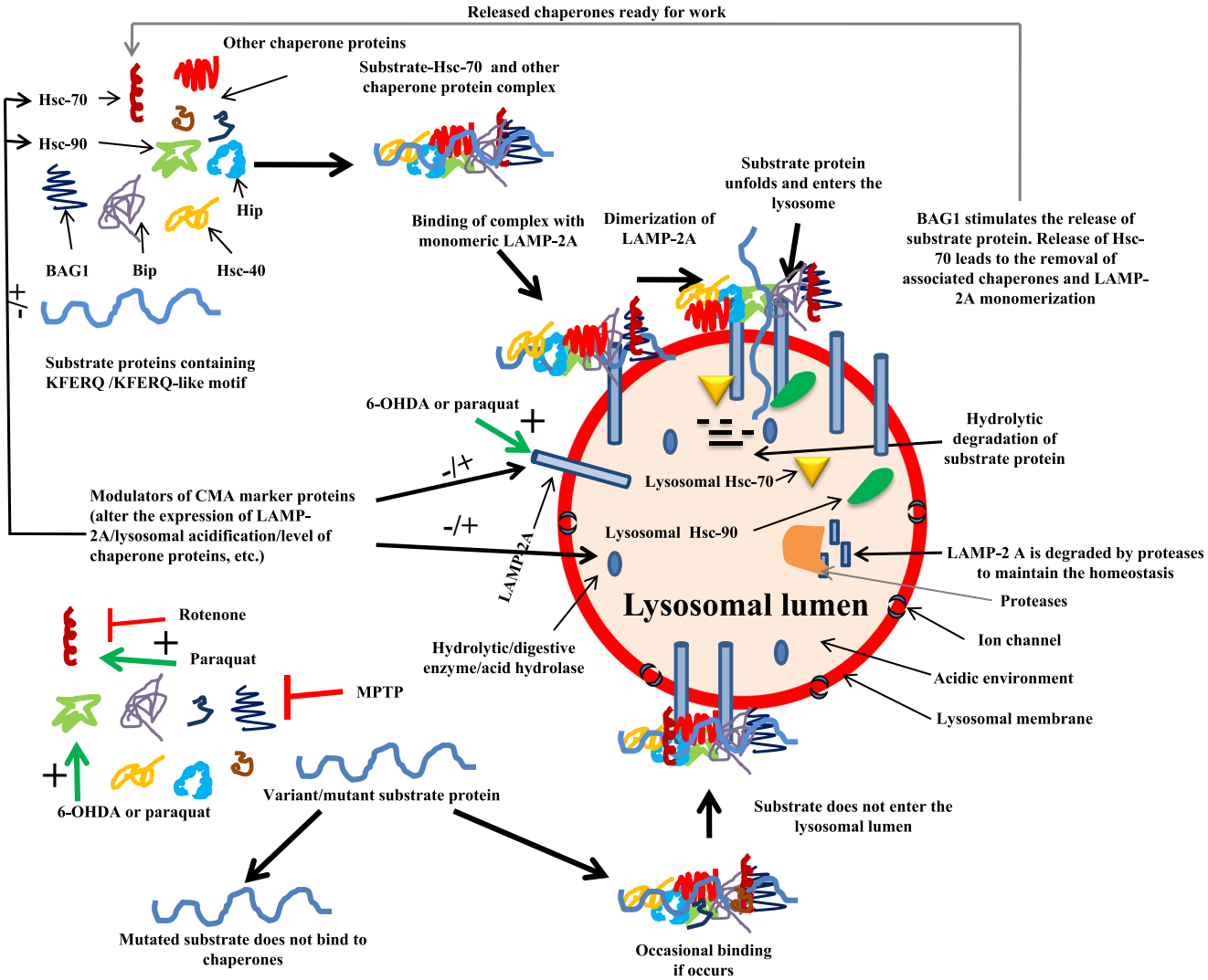

Fig. 1 Diagrammatic representation of CMA in the nigrostriatal pathway of the brain: A substrate protein containing KFERQ/KFERQ-like motif is recognized by Hsc-70 in the cytosol and leads to the formation of substrate-chaperone complex in the presence of a few other molecular chaperones. The substrate-Hsc-70 complex gets attached with monomeric LAMP-2A leading to its dimerization. Unfolding and release of the substrate in the lysosomal lumen are mediated by BAG-1. Degradation of substrate protein occurs by hydrolytic enzymes in the lysosomal lumen. Cytosolic and lysosomal Hsc-70 helps in the release of other molecular chaperones. Other molecular chaperones can perform their usual function in the cytoplasm once released from the complex. In order to maintain the homeostasis, LAMP-2A also enters the lumen and gets degraded by proteases, such as cathepsin A. Parkinsonian toxin 6-OHDA or paraquat induces LAMP-2A and Hsc-90, and paraquat also induces Hsc-70 levels. Rotenone attenuates Hsc-70 while MPTP decreases BAG-1 levels. Oxidative stress and modification in KFERQ/KFERQ-like motif or single nucleotide polymorphism in the substrate protein-coding gene alter the ability of substrate to form complex with Hsc-70. Mutation/polymorphism alters the conformation/interaction of substrate protein with LAMP-2A. It also alters the release of substrate in the lumen even if binding occurs. Modulators alter the expression/level of a few selected CMA markers, molecular chaperones or lysosomal acidification (Sala et al. 2016; Mishra et al. 2015; Cai et al. 2015; Agarraberes and Dice 2001; Kiffin et al. 2004; Kermer et al. 2015; Cai et al. 2015; Cuervo et al. 2003; Cuervo and Wong 2014; Wang et al. 2017; Murphy et al. 2015; Moors et al. 2017; Kiffin et al. 2004; Kermer et al. 2015; Saftig and Klumperman 2009; Kabuta et al. 2008)

acidic degradation of redundant proteins in the lysosome, an acidification inhibitor, bafilomycin A1, is found to inhibit CMA. Ammonium chloride inhibits protein degradation by the lysosome and acts as a CMA inhibitor (Zhang et al. 2014). While it does not affect Hsc-70 level, it is found to increase α-synuclein, MEF2D, and LAMP-2A levels (Sala et al. 2013). Besides, chloroquine that inhibits acidification also inhibits CMA and its indicators (Chaanine et al. 2015). While bafilomycin A1, ammonium chloride, and chloroquine are found to alter the CMA, the inhibitory effect could be non-specific since such agents are general lysosomal inhibitors and are also shown to inhibit other forms of autophagy. Methylene blue is reported to inhibit the chaperone activity required for CMA (Wang et al. 2010). Chemical entities that alter the expression of Hsc-70, Hsp-90, etc., are found to produce non-specific effects since these molecules perform multiple

cellular functions (Cuervo and Wong 2014). While several studies are performed employing autophagy inhibitors under various pathophysiological and experimental conditions and chronic diseases, such studies are limited in PD.

Macroautophagy activators usually produce minimum or negligible effects on CMA marker proteins (Finn et al. 2005). Therefore, CMA inhibitors have been synthesized for producing the protective effects in PD models. 6-Aminonicotinamide, a well-known inhibitor of glucose-6-phosphate dehydrogenase enzyme, is shown to activate CMA. On the other hand, Hsp-90 inhibitor, geldanamycin, inhibits chaperone activity and leads to CMA activation. Ordinary laboratory chemicals, such as hydrogen peroxide and mycophenolic acid are also found to activate CMA (Kiffin et al. 2004; Finn et al. 2005; Dohi et al. 2012). Malfunctioning of the lysosomal enzyme, glucocerebrosidase, is associated with increased PD risk (Ambrosi et al. 2015; Richter et al. 2014; Mcneill et al. 2014). Single nucleotide polymorphism in its coding gene gives rise to variant form of enzyme. Variant glucocerebrosidase possessing reduced enzyme activity shrinks the transport of α-synuclein for clearance through CMA (Ambrosi et al. 2015). An interaction between lysosome and α-synuclein transport could be improved by increasing glucocerebrosidase activity through diverse chemical agents including acid nanotized chemical entities, ambroxol and isofagomine (Ambrosi et al. 2015; Richter et al. 2014; Mcneill et al. 2014; Bourdenx et al. 2016). Most of the agents reported to alter the level of the selected CMA markers are non-selective in nature. Perhaps, such agents could not be used with conviction to prove the role of CMA in PD. Such agents could reduce an accumulation of redundant α-synuclein and motor features owing to restoration of the lysosomal function and acidification (Ambrosi et al. 2015; Richter et al. 2014; Mcneill et al. 2014). A few agents that modulate CMA marker protein LAMP-2A are found to partially rescue from PD progression. While effect of such agents is reported in a few cellular models of Parkinsonism, only limited studies are available in rodent models and perhaps no study is available in which any CMA marker protein or lysosomal acidification modulator is tested in clinics (Su et al. 2016; Zhu et al., 2014; Ambrosi et al. 2015; Bourdenx et al. 2016; Moors et al. 2017). Moreover, modulators of CMA indicators could be imperative in reducing the PD progression but translation value is still missing and needs further investigation.

Reality, Hype, and Myth Regarding the Fine-Tuning of CMA and Protection from PD

CMA is primarily regulated by the cytosolic chaperones and lysosomal acidity, membrane-bound proteins, and hydrolytic enzymes. It is commonly seen that the expression/activity of at least one variable mentioned in the preceding sections is compromised in Parkinsonism (Kermer et al. 2015; Alvarez-Erviti et al. 2010; Wang et al. 2017; Sala et al. 2013; Marin and Aguilar 2011). The level of CMA specific variables is modulated in part through particular inhibitors/enhancers (Finn et al. 2005). While the condition is hypothetically close to reality, pragmatic position is poles apart like chalk and cheese. Several modulators have been found to be effective in regulating the level of selected CMA marker proteins in cellular models (Su et al. 2016). Most of such modulators have not yet been tested in rodent models. Discrepancy in the level of neuroprotection is also not tested across various cellular models. It is also not known if the same modulator would offer the similar/dissimilar results in two identical cellular or rodent models. Such disparity is expected owing to the variable response of animals towards two divergent chemicals altogether (a modulator and a toxicant used to induce Parkinsonism) due to erratic chemical-chemical interaction and time, route, and dose of exposure. Moreover, the stage and state of defect in CMA are also critical. In a few cases, CMA is compromised at the level of substrate-chaperone complex due to inconsistent expression of proteins (Kermer et al. 2015; Liu et al. 2016; Wang et al. 2017; Sala et al. 2013; Marin and Aguilar 2011; Kowall et al. 2000). Malfunctioning of CMA could also be due to the presentation of substrate-chaperone complex to LAMP-2A. Occasionally, transportation of substrate to the lysosomal lumen or its acidification could also be defective. A CMA modulator is albeit useful in rectification of the selected CMA marker proteins; studies are required to identify and develop the novel CMA modulator that could be effectively employed against sporadic PD/PD models. Undeniably, sufficient progress has been made in identifying and characterizing defective steps of CMA in Parkinsonism; not even a single modulator is tested in all established cellular/animal models and sporadic PD. While encouraging observations have shown buoyancy, much embroidery could be seen. Similar to elusive PD pathogenesis, contributory factors, and permanent cure, application of modulators in CMA correction seems to be in the beginning stage and necessitates all-embracing studies. As of now, propaganda seems to be predominant over the reality albeit a few benefits have been observed.

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Compliance with Ethical Standards

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