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Review

Chaperone-mediated autophagy: Advances from bench to bedside

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ABSTRACT

Protein homeostasis or proteostasis is critical for proper cellular function and survival. It relies on the balance between protein synthesis and degradation. Lysosomes play an important role in degrading and recycling intracellular components via autophagy. Among the three types of lysosome-based autophagy pathways, chaperone-mediated autophagy (CMA) selectively degrades cellular proteins with KFERQ-like motif by unique machinery. During the past several years, significant advances have been made in our understanding of how CMA itself is modulated and what physiological and pathological processes it may be involved in. One particularly exciting discovery is how other cellular stress organelles such as ER signal to CMA. As more proteins are identified as CMA substrates, CMA function has been associated with an increasing number of important cellular processes, organelles, and diseases, including neurodegenerative diseases. Here we will summarize the recent advances in CMA biology, highlight ER stress-induced CMA, and discuss the role of CMA in diseases.

1. Introduction

Many critical cellular processes including maintaining viability depend on strict protein homeostasis, namely proteostasis (Amanullah et al., 2017; Taylor and Dillin, 2011). This is particularly important for the long-lived postmitotic cells such as neurons (Amanullah et al., 2017; Hekmatimoghaddam et al., 2017). Cellular proteostasis requires a constant balance between protein synthesis and degradation. Several types of machinery are specialized in the recognition and removal of unwanted proteins to ensure protein quality control. Chiefs among them are specific individual proteases, ubiquitin-proteasome system, and lysosome dependent autophagic process (Wen and Klionsky, 2016). Among the three forms of autophagy, chaperone-mediated autophagy (CMA) is distinct from macroautophagy (MA) and microautophagy in that it does not require the formation of vacuoles and only degrades selected individual proteins. Thus, CMA plays a particularly important role in protein quality control under both physiologic and pathologic stress conditions to guard proteostasis (Bejarano and Cuervo, 2010; Cuervo and Dice, 1998).

Cells experience constant physiologic and pathologic stresses. These stresses lead to protein damages. Many such stress conditions including nutrient-deprivation, oxidative stress, proteotoxicity, and lipotoxicity activate CMA, making CMA one of the primary machinery that respond to cellular needs to handle the stress (Gong et al., 2017; Patel and Cuervo, 2015). Coupled with the realization that nearly 30% cytosolic proteins may potentially be targeted by CMA as substrates (Dice, 2007), this has spurred a growing interest and substantial increase in CMA research since we published our first review article on CMA (Li et al., 2011). This has led to some significant advances in our understanding of CMA biology and its potential role in diseases. Here we will summarize some of the recent discoveries on CMA, highlighting, in particular, the regulation of CMA by stress and its involvement in neurodegenerative diseases.

2. Basic process and major discoveries of CMA

CMA is a multistep process via which lysosomes select and degrade cytosolic proteins. Although the CMA pathway was initially described only in mammal cells, the CMA component LAMP2A spliced variant has been discovered in birds (Patel and Cuervo, 2015), and the functional process equivalent to CMA is recently extended to lower species including fish (Yabu et al., 2011), Drosophila (Mukherjee et al., 2016), and *C. elegans* (Eisermann et al., 2017). CMA is distinct from the other two lysosome-based autophagy pathways, MA, and microautophagy, with its unique machinery and a non-vacuole-based mechanism. The basic process of CMA involves the following: first, it needs a cytoplasmic complex of chaperone proteins including heat shock cognate 70 kDa protein (Hsc70); second, chaperone Hsc70 selectively recognizes and interacts with cytosol proteins via their KFERQ-like motif (s); and third, the substrate and Hsc70 complex interacts with the receptor lysosome-associated membrane protein 2A (LAMP2A) (Kaushik and Cuervo, 2012); and this interaction drives LAMP2A oligomerization

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and substrate translocation into the lysosomal lumen for degradation. The highlights in the discovery of CMA are summarized below.

Lysosomes, discovered and named by Dr. Christian de Duve in 1955 (de Duve, 2005), are membrane-bound organelles involved in various cell processes including degradation of unwanted materials in the cytoplasm, cell signaling, energy metabolism, secretion, and plasma membrane repair (Luzio et al., 2014). Degradation of proteins by lysosomes was initially believed to be non-specific (Bird et al., 1977; Libby and Goldberg, 1978). But in the 1980s, Dice's group demonstrated that lysosomes are also involved in a pathway for specific protein degradation. In 1982, Dice's laboratory reported that radiolabeled ribonuclease A (RNase A) introduced into the cytoplasm of human fibroblasts is degraded with a half-life of approximately 90 h in the presence of serum. However, serum deprivation increased the rate of degradation by 1.6-fold (Dice, 1982). Later, they showed that this degradation depends on both lysosomes and a specific motif in RNase A. These findings revealed that lysosomes might selectively degrade a subset of proteins and provided the initial clue for the presence of a lysosome-based selective degradation process, which was later renamed as CMA (Dice et al., 1987; Kiffin et al., 2004). The second major discovery is the identification of the KFERQ-like motif as the signature for CMA substrates. The enhanced breakdown of RNase A following serum withdrawal was found to be dependent on a feature of its N-terminal 20 amino acids. The pentapeptide sequence related to KFERQ was identified as the signature motif required for proteins being selectively removed by this degradation pathway (Dice et al., 1986). In 1989, Hsc70 was found to bind to the KFERQ-like region of intracellular proteins targeted for lysosomal degradation in response to serum deprivation. This became the first chaperone protein as well as the most common one identified for CMA process (Chiang et al., 1989). In 1996, LAMP2A, also named Lgp96 (lysosomal glycoprotein of 96 kDa), was identified as a protein needed for the selective import and degradation of proteins within lysosomes, defining LAMP2A as the receptor for CMA (Cuervo and Dice, 1996). In 1997, Hsc70 was found in the lumen of lysosomes and determined to be required for this lysosome-mediated selective protein degradation (Agarraberes et al., 1997). The intra-lysosomal level of Hsc70 is now considered to be a marker directly reflecting CMA activity. The term “chaperone-mediated autophagy” was coined by Dr. Dice in 2000 when he for the first time used CMA instead of “the lysosome-based selective degradation” to report the decline of CMA in aging tissues and cells, revealing the possibility that this newly-identified cellular process may be involved in age-related diseases (Cuervo and Dice, 2000a). One of the early findings on how CMA may be regulated is the realization that the dynamic distribution of LAMP2A between the lysosomal matrix and membrane contributes to the regulation of LAMP2A (Cuervo and Dice, 2000b), and the realization that LAMP2A turnover is regulated by cathepsin A (Cuervo et al., 2003). Furthermore, the dynamic change of LAMP2A from monomer to oligomer is necessary for the CMA activity and process (Bandyopadhyay et al., 2008). As for the role of CMA in neurodegenerative diseases, two independent Science reports described that α-synuclein is a substrate for CMA and impairs CMA-dependent regulation of a neuronal factor MEF2D required for the survival in dopaminergic neurons (Cuervo et al., 2004; Yang et al., 2009), presenting the first set of evidence for CMA implicated in Parkinson's disease (PD) and spurring tremendous interest in the investigation of CMA in diseases. Two disease areas where the most significant advances have been made are neurodegenerative diseases and cancer. One recent study identified phosphorylation of LAMP2A by p38 MAPK as a key and direct mechanism to activate CMA and maintain proteostasis under ER and PD associated stress (Li et al., 2017a). This is the first demonstration of a pathway that specifically signals from ER to CMA (see below) in response to a variety of stress conditions including pathogenic stress associated with PD.

Other advances that should be noted include progress toward the development of research tools. One advance is the development of a photoconvertible fluorescent-based technique to track CMA and monitor its activity in cells. The activity of CMA is traditionally measured in vitro using isolated lysosomes. But these techniques are not suitable for studying CMA in living cells. To overcome the limitation, the Cuervo's team developed a photoconversion-based fluorescence technique to image and quantify CMA activity in living cells (Koga et al., 2011b). They introduced a KFERQ-related motif into fluorescent proteins (CFP and mCherry), which converts these two proteins into CMA substrates. The fluorescent intensity of the monomeric proteins is not impacted by MA. This allows the measurement of dynamic changes of CMA activity in living cells by following the distribution of the photoconverted fluorescent signal. The second advance is the identification of the derivatives of all-trans-retinoic acid as small molecule activators of CMA, providing additional chemical tools for activating CMA. Cuervo's group reported that retinoic acid receptor (RAR) signaling and all-*trans*-retinoic acid (ATRA, a natural activator for RAR) exert an inhibitory effect on the CMA activity (Anguiano et al., 2013). On the contrary, RAR antagonists derived from retinoids have a stimulatory effect on CMA. Since compromise of CMA has been reported in several age-associated diseases including neurodegenerative disorders and diabetes (Arias, 2017), RAR antagonists may be potential drug candidates for CMA-compromised diseases.

3. Major mechanisms that regulate CMA

Like many other cellular processes, CMA also responds robustly to extracellular and intracellular signal clues including stress, and therefore its activity is tightly regulated. Both the regulatory targets along the CMA process as well as pathways mediating the regulatory signals are of fundamental importance. Recent advances have both expanded the points of regulation and revealed new signaling pathways that modulate CMA activity.

3.1. Regulation of LAMP2A

LAMP2A level and assembly at lysosomal membrane is the rate-limited step for the CMA process. Several recent studies shed new light on how LAMP2A trafficking and stability may be regulated. The deficiency of the cystine transporter cystinosin causes the lysosomal storage disease cystinosis, which is characterized by cell malfunction and progressive renal injury. Cystinosis is associated with defects in CMA and impaired LAMP2A trafficking and localization. The LAMP2A trafficking defect could be rescued by cystinosin, the small GTPase Rab11, and Rab7 effector RILP (Zhang et al., 2017). PARK7/DJ-1 plays an important role in antioxidative response, and its gene mutation is associated with autosomal recessive familial PD (Canet-Aviles et al., 2004). CMA has been shown to degrade the oxidatively damaged nonfunctional PARK7/DJ-1 (Wang et al., 2016). Interestingly, a recent study showed that PARK7/DJ-1 deficiency correlates with a loss of LAMP2A upregulation upon stress. PARK7/DJ-1 appears to increase LAMP2A stability since its deficiency is associated with accelerated degradation of LAMP2A by the lysosomes (Xu et al., 2017). These findings provide new lines of evidence for additional factors engaged in regulating LAMP2A, reinforcing the notion that LAMP2A is the key regulator of the CMA process.

3.2. Regulation of chaperones

Humanin (HN) is a mitochondria-associated peptide and possesses protective activity in several cell lines and cultured primary cardiomyocytes and cortical neurons. Interestingly, this protective activity is lost in CMA-deficient cells. Humanin is shown to increase the binding of CMA substrates with and their translocation into lysosomes. This appears to involve heat shock protein 90 (HSP90). Humanin interacts with HSP90 at the cytosolic side of the lysosomal membrane and stabilizes the interaction of the chaperone with CMA substrates, thus facilitating the lysosomal translocation of substrates (Gong et al., 2017). Thus,

together with the findings above, they indicate that multiple points of regulation exist to ensure the overall efficiency of CMA.

LAMP2C, one of three LAMP2 splicing isoforms, is more limited in its expression compared with the broad presence of LAMP2A and LAMP2B in many tissues. In B cells, increased LAMP2C expression has been shown to specifically perturb the cytoplasmic MHC class II antigen presentation via CMA but not MHC class II presentation of epitopes from exogenous and membrane antigens. The LAMP2C level can modulate the steady-state levels of several cytoplasmic proteins that are targeted for degradation by CMA. This appears to involve impairing the association between cytoplasmic substrate proteins and Hsc70 (Perez et al., 2016). Thus, LAMP2C may function as an endogenous inhibitor of CMA in B cells in part by interfering Hsc70 function.

3.3. Signal pathways regulating the activity of CMA

Two major signaling pathways have been identified to modulate CMA process directly or indirectly. They are the mammalian target of rapamycin C2 (mTORC2)-Akt pathway targeting glial fibrillary acidic protein (GFAP) and direct phosphorylation of LAMP2A by lysosomal p38 MAPK following ER stress.

3.3.1. Regulation of CMA by mTORC2-Akt

mTOR is a serine/threonine kinase and functions as a key cellular nutritional sensor in response to the alteration in growth factors, energy levels, cellular stress, and amino acids. mTOR has two distinct complexes, mTORC1 and mTORC2. The extensive study has shown that MA is inhibited by the activation of lysosomal mTORC1 (Rabanal-Ruiz et al., 2017). Interestingly, mTORC2 has been identified as a negative regulator of CMA. It is shown that the mTORC2-lysosomal Akt cascade inhibits the assembly of LAMP2A and the activity of CMA in part by phosphorylating GFAP, a positive regulator of CMA. The starvation condition causes the recruitment of the phosphatase PHLPP1 to the lysosomes and inhibition of Akt, increasing the stability of the LAMP2A-based translocation complex and enhancing the activity of CMA (Arias et al., 2015). Consistently, in acute liver failure model, the activation of PI3K/Akt/mTOR pathway correlates with a decrease in LAMP2A and Hsc70 (Li et al., 2017b).

3.3.2. Regulation of CMA by ER stress

ER and lysosomes are two primary cellular organelles responsible for processing stress signals and executing a range of proper responses. ER disturbance triggers unfolded protein response (UPR), which is aimed at reducing ER work loading and increasing its capacity for protein folding, processing, and ER-associated degradation (ERAD). Several distinct pathways including PERK [double-stranded RNA-activated protein kinase (PKR)-like ER kinase] regulate UPR. The initial UPR promotes an adaptive mechanism to restore ER homeostasis and maintain cellular viability, but when ER stress becomes insurmountable, UPR also leads to apoptosis (Walter and Ron, 2011). Many studies have shown that ER stress activates MA, but whether and how ER stress induces CMA remains completely unexplored. In a recent article, we uncovered a novel pathway that senses and transmits ER stress to p38 MAPK and activate CMA via LAMP2A (Li et al., 2017a) (Fig. 1). We showed that multiple ER stressors lead to a PERK-dependent activation and recruitment of MKK4 to the lysosomes, activating a lysosomal pool of p38 MAPK. Lysosomal p38 MAPK directly phosphorylates the CMA receptor LAMP2A at T211 and T213. This dual phosphorylation modification constitutes a key regulatory event in modulating the LAMP2A level and oligomerization on the lysosomal membrane. This is the first example demonstrating that signal-mediated posttranslational modification of LAMP2A regulates its function. We have termed the coupling between ER stress and CMA *ERICA* for ER stress-induced chaperone-mediated autophagy. Engaging ERICA is functionally required for maintaining cellular homeostasis and protecting cells from initial stress while uncoupling it is associated with increased neuronal death in vivo in a neurotoxin-induced model of Parkinson's disease. Our data indicate that the coupling between ER and CMA is unexpectedly tight since all the ER stressors which we tested trigger ERICA. Thus, ER stress response and CMA are highly coordinated processes, raising important questions of whether recruiting CMA is obligatory for cells to adequately handle ER stress, how ERICA and ERAD may be co-regulated and cooperate in mediating proteostasis, and whether other non-UPR signals may also engage this pathway or part of it to modulate CMA. Answers to these questions will help establish the role of ERICA in a broader range of cellular processes and responses. Our findings indicate that ER stress employs distinct UPR transducers, PERK and IRE1, to trigger CMA and MA, respectively (Li et al., 2017a; Ogata et al., 2006). Thus, the identification of ERICA offers the possibility of selectively manipulating CMA over MA, which may be explored for the development of novel therapeutic strategies to specifically target CMA in diseases associated with CMA defects.

4. Dysregulation of CMA in diseases

With CMA being shown to participate in increasingly more cellular processes, it should not come as a surprise that there is a growing recognition that dysfunction of CMA contributes to diseases. Among them, neurodegenerative diseases and cancer have received the most attention. Given the scope of the journal, we will focus primarily on the findings linking CMA and neurologic disorders.

4.1. CMA and neurodegenerative diseases

Neurons are post-mitotic cells and require efficient protein degradation machinery to cope with the pressure (Hara et al., 2006; Rubinsztein, 2006). If not removed, unfolded or damaged proteins are often prone to aggregate, a distinct feature of many neurodegenerative diseases. Evidence has shown that CMA is constitutively active in neurons. CMA activity can be robustly up-regulated in response to diverse neurotoxic assaults (Cuervo et al., 2004; Gao et al., 2014; Yang et al., 2009), which plays an important role in relieving the burden caused by unfolded and damaged proteins. CMA dysfunction has now been implicated in the pathogenic process of several major neurodegenerative diseases.

4.1.1. Parkinson's disease (PD)

Gradual loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) is the main pathological feature of PD. The underlying mechanisms of such selectivity remain to be identified (Dauer and Przedborski, 2003). Several lines of evidence indicate that CMA may be involved in PD pathogenesis. Evidence from postmortem analysis shows that the level of LAMP2A protein is lower in the brain tissues of PD patients than in controls, suggesting that the activity of CMA may be impaired in PD (Alvarez-Erviti et al., 2010; Murphy et al., 2015). The well-known key component of Lewy bodies (cytoplasmic inclusion in the SNc neurons), α-synuclein, has been shown to be degraded through the CMA pathway. Moreover, mutant forms of α-synuclein (A53T or A30P), which cause familial PD, bind LAMP2A with a higher affinity but are poorly translocated into the lysosomes, which has been proposed to interfere with the normal degradation of other CMA substrates (Cuervo et al., 2004; Martinez-Vicente et al., 2008). Interestingly, interfering CMA appears to be a common mechanism for several pathogenic mutants which have been associated with familial PD. Leucine-rich repeat kinase 2 (LRRK2) G2019S mutation is the most common cause of autosomal dominant familial PD (Correia Guedes et al., 2010). Both wild-type and G2019S mutant LRRK2 can be recognized by the CMA machinery. However, the G2019S mutant has been shown to inhibit the dynamic assembly of the CMA translocation complex at the lysosome membrane, leading to the disruption of the CMA process (Orenstein et al., 2013). Mutant of ubiquitin C-terminal hydrolase L1 (UCHL1), which increases PD susceptibility (Ardley et al., 2004),

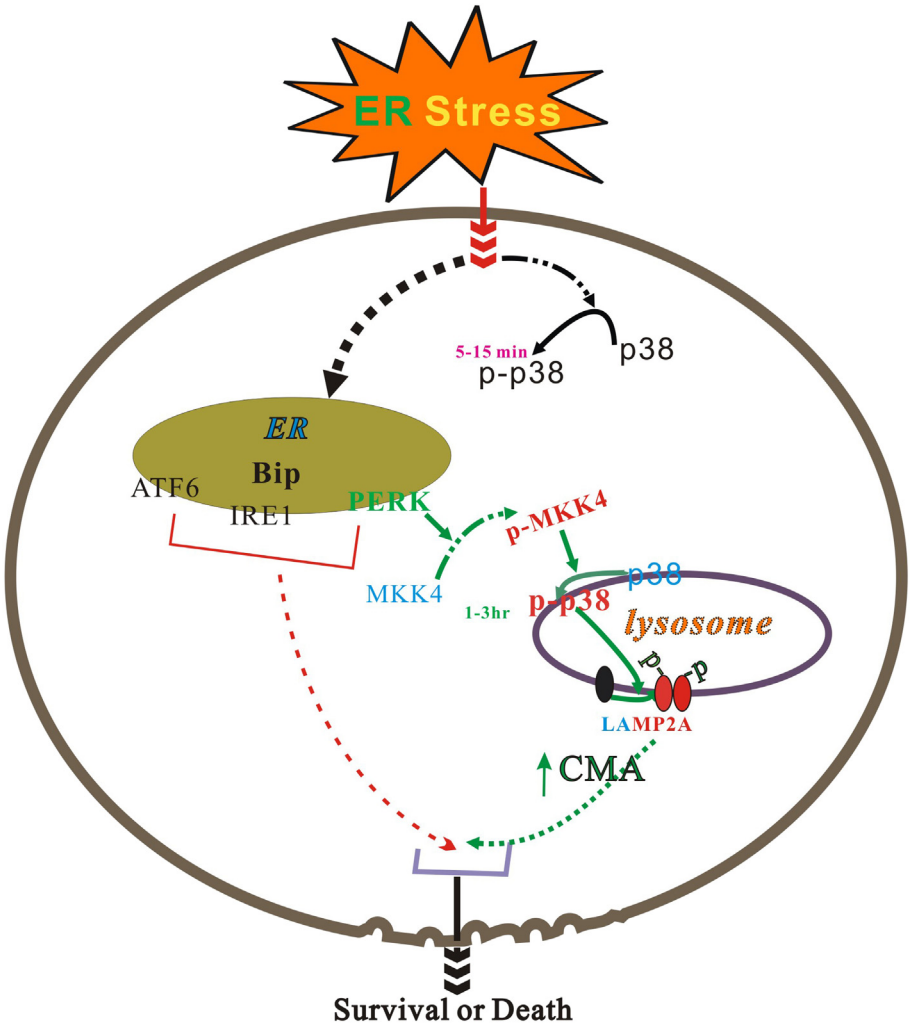

Fig. 1. MAPK p38 links ER stress to CMA. ER stress can induce CMA and activate multiple pathways including the short transient activation of p38 MAPK pathway with a peak of 5–15 min and three UPR pathways. Among three main UPR transducers, only PERK can increase phosphorylation of MKK4 and drive the active MKK4 (p-MKK4) translocate to lysosomes where it can activate p38 MAPK with a peak of 1–3 h following the stress. The activated p38 can directly phosphorylate LAMP2A at T211 and T213 sites and increase its activity for CMA, which has a protective role against cell death during the process of ER stress while the final fate of cells is decided by the balance between survival and death forces.

interferes with CMA (Kabuta et al., 2008). Similarly, mutation of glucocerebrosidase (*GBA1*) gene can also impair the CMA activity, causing aberrant proteostasis and accumulation of α-synuclein (Kinghorn et al., 2017).

In addition to the defect in CMA flux summarized above, several additional mechanisms also modulate LAMP2A and may be relevant to PD. As indicated, our most recent study revealed a pathway termed *ERICA* by which ER stress leads to a p38 MAPK-dependent dual phosphorylation of LAMP2A, which activates LAMP2A (Li et al., 2017a). Uncoupling *ERICA* pathway has been shown to sensitize SNc DA neurons to stress and maintaining adequate CMA activity by *ERICA* is critical for protecting SNc DA neurons in response to ER stress and neurotoxic insult in the model of PD. Vacuolar protein sorting-35 (VPS35) is essential for endosome-to-Golgi retrieval of LAMP2A in DA neurons. VPS35 mutation (D620N) impairs this retrieval process in mice and is associated with accelerated LAMP2A degradation and exacerbated α-synuclein accumulation (Tang et al., 2015). Post-translational modifications and regulation of LAMP2A trafficking may represent an important regulatory mechanism critical for the control of CMA, and their defect may sensitize SNc DA neurons to stress.

Although it was proposed that loss of CMA under pathogenic stress as demonstrated above might undermine the viability of SNc DA neurons in PD pathogenesis, direct mechanisms by which CMA might modulate neuronal survival remained to be established. Identification of transcription factor myocyte enhancer factor 2D (MEF2D) as a CMA substrate allowed the establishment of a more direct link between CMA and neuronal survival machinery. MEF2D has been shown to promote neuronal survival (Gong et al., 2003; Yang et al., 2009) including the survival of SNc DA neurons (She et al., 2011; Smith et al., 2006). We showed that the MEF2D is constantly shuttled to the cytoplasm and degraded by CMA. Homeostasis of MEF2D requires CMA, and this process is sensitive to and blocked by α-synuclein (Yang et al., 2009). Oxidized MEF2D, which loses its transactivation function, is preferentially cleared by CMA (Gao et al., 2014). Therefore, CMA promotes neuronal viability in part by maintaining MEF2D homeostasis. In support of this, CMA has recently been found to degrade oxidized F-box Protein Fbw7β, another protein involved in the survival of dopaminergic neurons (Wang et al., 2017).

Mitochondrial dysfunction has been implicated in the loss of SNc DA neurons in PD (Dawson and Dawson, 2003; Narendra et al., 2008). The SNc DA neurons require the high level of energy to support robust mitochondrial fission and fusion. This is accompanied by reactive oxygen species (ROS) production (Chen and Chan, 2009; Youle and van der Bliek, 2012). Adequate antioxidant capacity is needed to maintain mitochondrial health in SNc DA neurons. DJ-1/PARK 7 plays an important role in regulating mitochondria function and morphology. Mutation of *DJ-1* gene is believed to contribute to 1–2% autosomal recessive PD (Bonifati et al., 2003). Recent work has shown that DJ-1 is a CMA substrate (Wang et al., 2016). CMA actively participates in the surveillance and protection of mitochondrial function by maintaining an appropriate pool of functional DJ-1. Interruption of the CMA-DJ-1 pathway leads to excessive mitochondrial damage and ROS production under stress (Wang et al., 2016). These findings establish a close link between CMA and mitochondrial quality control.

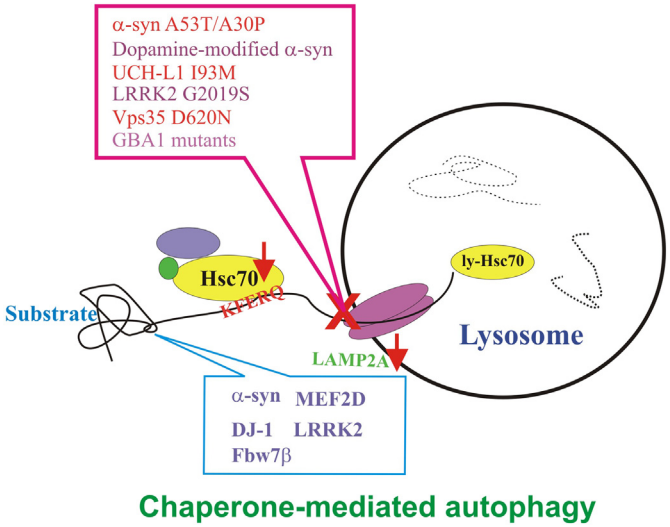

Fig. 2. The interplay of PD-associated proteins with CMA. The activity of CMA reduces in specific PD-related brain regions under various PD condition. Several PD-associated proteins as indicated in the blue box have been identified as substrates of CMA, and the degradation decrease of these proteins occur under PD conditions, leading to either aggregation or dysfunction of proteins. On the other hand, mutant or deficient PD-associated proteins indicated in the red box can directly or indirectly dysregulate LAMP2A, leading to the reduction of CMA activity, which may be implicated in the pathogenesis of PD. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Thus, both genetic and neurotoxic stressors associated with PD cause CMA impairment. Although their strength may vary, multiple lines of evidence indicate consistently that such impairment is a pathogenic feature in cellular and animal PD models as well as human specimens. The intricate functional interplays between CMA and multitude of organelles including the nucleus, mitochondria as well as ER may be altered under PD associated stress and may underlie PD pathogenesis. The interplay between these factors and CMA in PD is summarized in Fig. 2.

4.1.2. Alzheimer's disease (AD)

AD is the most common neurodegenerative disorder. Loss of proteostasis, evidenced by β-amyloid plaque formation and tau aggregation, is considered to be the basis of AD pathogenesis. Tau pathology is, at least in part, the consequence of aberrant turnover (Scheltens et al., 2016). How tau and its fragments are cleared by neurons remains controversial (Iqbal et al., 2009; Min et al., 2010; Petrucelli et al., 2004). There is evidence for the degradation of wild-type (WT) tau through the CMA pathway (Caballero et al., 2017). The tau mutants P301L and A152T appear to hinder the uptake of WT tau. But interestingly, they interfere with CMA by distinct mechanisms. A152T mutant tau binds to the lysosomal membrane with a higher affinity but is translocated into the lumen with a slower rate, thus competing with WT tau for LAMP2A. However, the P301L mutant does not accumulate at the lysosomal membrane. Instead, the pathogenic protein substantially represses the CMA activity induced by numerous stress conditions (Caballero et al., 2017). Tau can be cleaved into different fragments (F1, F2, and F3) in neurons. The generation of F1 occurs by a cytosolic protease. F1 is delivered to the lysosomes to be processed by the lysosome enzyme cathepsin L, generating tau fragments F2 and F3 that are capable of seeding the aggregation of Tau. Delivery of F1 fragment to the lysosome requires CMA. However, the F1 fragment does not appear to enter lysosomes fully. This may promote Tau oligomerization at the lysosomal membrane, thereby inhibiting the dynamic assembly of CMA machinery and the digestion of other substrates (Wang et al., 2009).

4.1.3. Huntington's disease (HD)

HD is a late-onset neurodegenerative disorder marked by uncontrolled movement, dementia, and emotional disturbance. The nuclear aggregates composed of mutant huntingtin with expanded repeats of polyglutamine (polyQ) residues are the pathologic hallmark of HD. Toxicity caused by huntingtin aggregates is thought to underlie HD pathogenesis and represents a promising therapeutic target for the disease (Bates, 2003). Previous studies have shown that CMA is involved in the degradation of mutant huntingtin. Huntingtin harbors putative KFERQ motif and interacts with the key components of CMA, Hsc70, and LAMP2A. Moreover, mutant huntingtin with an expansion of the polyQ tract displays impaired uptake by CMA (Qi and Zhang, 2014; Qi et al., 2012). Post-translational modifications, such as phosphorylation and acetylation, influence the degradation of huntingtin by CMA via changing the charge properties of the KFERQ-like pentapeptide (Thompson et al., 2009). In addition to CMA, MA and proteasome also participate in the regulation of huntingtin turnover (Qin et al., 2003). The detailed mechanisms about how neurons respond to huntingtin aggregates via these various processes need to be further elucidated. Interestingly, components of CMA (LAMP2A and Hsc70) are upregulated in cellular and animal models of HD in the initial stage of the disease. But LAMP2A level decreases during the late stage of the disease. The early increase in CMA components may represent a compensatory response to the inhibition of MA by huntingtin mutant to restore proteolytic homeostasis. However, the decline in the level of lysosome LAMP2A indicates that there is a loss of CMA function in the late phase of HD (Koga et al., 2011a). Further investigation into the biphasic change in CMA activity should provide important information on how CMA may be dynamically regulated under stress conditions in neurons and diseases.

4.2. Cancer

Although there is a substantial body of literature on CMA and cancer (Galan-Acosta et al., 2015; Tang et al., 2017), the precise role for CMA in cancer is still under debate. Findings from some studies are consistent with the idea that CMA enhances the development of certain cancers. But there is also increasing evidence demonstrating that CMA can inhibit cancer by specifically degrading tumor promoters.

On the one hand, CMA appears to be required for cancer cell proliferation in vitro because it contributes to the maintenance of the metabolic alterations characteristic of malignant cells (Kon et al., 2011). LAMP2A is elevated in breast tumor tissues, particularly in metastatic carcinoma (Han et al., 2017). LAMP2A knockdown significantly inhibits the growth and metastasis of breast cancer cells in vivo and in vitro while upregulation of CMA activity by LAMP2A overexpression has the opposite effect. By an unknown mechanism, CMA-defective cancer cells exhibit increased activation of the tumor suppressor p53, which is associated with cell cycle arrest, increased apoptosis, and reduced glycolytic metabolism in tumor cells (Wu et al., 2017a). Inhibition of CMA induces the regression of existing human lung cancer xenografts, delays xenograft tumor growth, and reduces the number of cancer metastases in mice (Kon et al., 2011). On the other hand, CMA has also been shown to play a role of tumor suppressor by degrading specific tumor promoters. For example, CMA inhibits cellular transformation, cell proliferation, and colony formation by degradation of Myc (Gomes et al., 2017); inhibits lung cancer cell growth by degradation of MCL1 (Suzuki et al., 2017); and degrades mutant p53 (Vakifahmetoglu-Norberg et al., 2013). More studies need to work out the precise role of CMA in cancer.

4.3. Immune diseases

Increasing evidence shows that CMA displays an essential role in the homeostasis of immune cells, antigen processing and presentation, and many other immune processes (Wang and Muller, 2015). For example,

CMA pathway plays pivotal functions in major histocompatibility complex class II-mediated processing and presentation of several endogenous antigens by transporting them from the cytosol to lysosomal compartments (Wang and Muller, 2015), and contributes to herpes viral antigen presentation (Taylor et al., 2011). Interestingly, perturbation of CMA is implicated in the autoimmune disorder lupus (Ruiz-Cerda et al., 2016). The level of LAMP2A and CMA activity are increased in lupus B cells, providing a potential approach for the lupus therapy (see below) (Macri et al., 2015). CMA is also implicated in response to microbe infection. BCL2 associated athanogene 3 (BAG3) is a co-chaperone of CMA and regulates cellular homeostasis. BAG3 alters the intracellular localization of filovirus protein VP40, reducing the budding of infectious virus. Thus, CMA function of BAG3 may represent a specific host defense to control the spread of virus particles (Liang et al., 2017). Salmonellae can replicate within host cells in the absence of exogenous glucose and amino acids. Intracellular Salmonellae recruit the host proteins LAMP2A and Hsc70, leading to the increase of CMA activity and host-derived peptides to promote the intracellular growth of Salmonella (Singh et al., 2017).

5. Targeting CMA for therapy

5.1. Neurodegenerative diseases

The effectiveness of enhancing CMA as a therapeutic strategy depends on the degree of defect of this delivery system in disease. As described above, defects of CMA function have been consistently observed in several major neurodegenerative disorders including PD, AD, and HD (Caballero et al., 2017; Yang et al., 2016). These provide the strong rationale for augmenting CMA to treat neurodegenerative disorders. Conceptually, several key regulatory steps in the entire CMA process may provide opportunities for modulating CMA activity therapeutically. Increasing the level of LAMP2A was shown to attenuate the decline of the liver function during aging in model animals (Zhang and Cuervo, 2008), providing the proof-of-concept that LAMP2A may serve as an effective therapeutic target. Similarly, augmenting LAMP2A level by recombinant adeno-associated virus protected dopaminergic neurons at the substantia nigra from α-synuclein induced degeneration (Xilouri et al., 2013). The challenge is to design selective and potent CMA modulators suitable for the central nervous system application. This area of research remains largely unexplored. On this note, it is encouraging to acknowledge that all-trans-retinoic acid derivatives, which inhibit retinoic acid receptor α, and humanin, as well as its analogues, have been shown as chemical and biological tools to modulate CMA, offering the initial examples for the hope of identifying more desirable CMA activators (Anguiano et al., 2013).

In addition to the level of LAMP2A, the discovery of ERICA provides several additional novel therapeutic targets for enhancing CMA. These new potential intervention points include LAMP2A phosphorylation, the lysosomal membrane p38 MAPK, and the link between PERK and MKK4. Since ERICA is highly specific for CMA, one expected advantage of modulating ERICA is the minimization of off-target effects on non-CMA processes. Given that ER stress is involved in the pathogenesis of several major neurodegenerative diseases (Wu et al., 2017b), targeting ERICA may be a promising therapeutic approach to lessen ER dysfunction-associated pathogenic stress.

Besides CMA, MA has also been shown to promote neuronal survival in many disease models by increasing the clearance of damaged proteins. For example, rapamycin, an autophagy enhancer, significantly reverses lactacystin-induced loss of nigral DA neurons in C57BL/6 mice (Pan et al., 2008). In addition, cerebral ischemic preconditioning reduces infarct volume, brain edema and motor deficits induced by permanent focal ischemia through activation of MA (Papadakis et al., 2013). Finally, rapamycin and nicotinamide phosphoribosyltransferase, the rate-limiting enzyme in mammalian NAD (+) biosynthesis, protect against ischemic stroke by inhibiting neuronal apoptosis and necrosis through the activating MA (Sheng et al., 2010; Wang et al., 2012). Therefore, therapeutically, enhancing CMA and MA may have complementary or synergistic effects in restoring proteostasis for diseases.

5.2. Other diseases

Unlike the loss of CMA in neurodegenerative diseases, abnormal upregulation of CMA activity may contribute to the pathogenesis of other diseases including immune disorders such as lupus (Wang and Muller, 2015). Lupuzor (P140), a 21-amino acid peptide generated from the spliceosomal U1-70K protein, is a drug candidate for lupus in Phase 3 clinical trial (Macri et al., 2015). Interestingly, the mechanism of action for P140 against Lupus involves CMA. P140 uses the clathrin-dependent endolysosomal pathway to enter B lymphocytes and accumulates in the lysosomal lumen where it may directly hamper lysosomal HSC70 chaperon function and also destabilize LAMP2A. This is believed to interfere with the endogenous autoantigen processing and loading to major histocompatibility complex class II molecules, which eventually reduces the activation of autoreactive T cells (Macri et al., 2015).

One potential challenge for CMA based therapeutics is the side effects of therapeutic activation of CMA. For example, although CMA is hyperactivated in lupus, a decrease in CMA may underlie the basis of defective T-cell function with age and immunosenescence. Thus, in principle, anti-CMA therapy may exacerbate T cell dysfunction, particularly in older patients. This concern is especially relevant to cancer therapy because both up- and down-regulation of CMA has been shown to be associated with cancers. Therefore, the value of targeting CMA in these diseases needs to be carefully evaluated.

6. Concluding remarks and remaining challenges

Compared to nearly 30 years ago when Dr. Dice's laboratory first discovered the process KFERQ-dependent process of selective protein degradation which was later named CMA, past decade has certainly witnessed tremendous growth in CMA related research. In spite of the advances, many challenges remain, some of which are highlighted below.

The research in the past decade has led to a significant expansion of the lists of CMA substrates, cellular processes which are modulated by CMA, and the pathological role of CMA in diseases. Even with the progress, there are significant challenges. For example, despite that more and more proteins have been identified as CMA substrates, our understanding of the capacity of CMA is far from completed considering that nearly 30% cytosolic proteins possess KFERQ-like motif in their sequence. One possible strategy to significantly accelerate the discovery is to employ systematic approaches to identify substrates under specific conditions. How CMA chooses to remove its substrates is not entirely clear. Does it degrade mostly misfolded proteins or target functional proteins for removal also? The findings that acetylation of a protein may convert it into a CMA substrate suggests that other mechanisms may exist to modulate substrate recognition (Lv et al., 2011). The notion that CMA substrate is purely governed by the accessibility to the primary KFERQ motif may need reconsideration.

One of the fundamental questions that have puzzled the field is whether LAMP2A is the only receptor for CMA. The question initially arose when it was shown that knockout of *lamp2* gene did not alter the activity of CMA in the animal (Eskelinen et al., 2004). This surprising observation was reinforced by another study in which samples of Danon disease show a reduced level of LAMP2A but the lysosomes have a normal level of CMA activity (Rothaug et al., 2015). Together, they highlight the need to understand if additional factors may serve to regulate CMA in the absence of LAMP2A.

Another issue is the relationship or interaction between CMA and other forms of autophagy. For instance, many signals are known to activate MA and CMA either sequentially or simultaneously. The

molecular mechanisms or pathways modulating the potential cross-talks between the two processes remain poorly understood. Also, there appears to be some overlap between endosomal-microautophagy (eMI) and classic CMA. eMI is dependent on the chaperone Hsc70 to target individual proteins with the KFERQ-like motif selectively (Tekirdag and Cuervo, 2017). Thus, it appears that eMI at least shares some of the regulatory component(s) with CMA. However, these two processes are distinctive. For instance, the processes happen at late endosome for eMI and lysosomes for CMA. Substrate unfolding is a pre-requisite for delivering substrate into the lumen of lysosome in CMA whereas folded proteins and even small oligomeric protein complexes can be internalized in the e-MI vesicles (Morozova et al., 2016; Tekirdag and Cuervo, 2017). LAMP2C, a splicing variant of *lamp2* gene that also encodes LAMP2A, functions as a receptor to mediate lysosome-dependent removal of RNA and DNA substrates (Fujiwara et al., 2013), extending the role of LAMP2 family proteins and raising the question of whether there may be potential cross-talks between protein and nucleic acid metabolism mediated by the close members of LAMP2 family.

To what degree the activity and regulation of CMA may be tissue-specific is unclear. This question arose because although it was reported that CMA activity declines in aging, some recent studies indicate that the relationship between aging and CMA may be more complex. For example, in rat nucleus pulposus, both LAMP2A level and CMA activity were found to be significantly higher in the 24-month old rat nucleus pulposus than in the 3-month group (Ye et al., 2011). Another group reported that LAMP2A increases in cardiac muscle but decreases in skeletal muscle during aging (Zhou et al., 2017). These new reports raise the possibility that aging-related changes of LAMP2A and CMA may be tissue-specific.

Understanding the precise changes of CMA under various pathogenic conditions and clarifying its roles in diseases remain an exciting area of CMA research. One of the promising disease areas where the evidence is perhaps the strongest is PD. Although the noteworthy progress has been made, additional effort is needed to validate the therapeutic efficacy of improving CMA in appropriate PD models and to develop more potent and specific strategies of modulating CMA in vivo. Given the complex involvement of CMA in diseases, how to target CMA therapeutically requires careful consideration. It is possible that for some diseases, modulating the entire CMA process may be beneficial. But for other pathologic conditions, it might be more desirable to target individual substrates relevant to the specific disease processes.

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