Review

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Roles of CMA in Neurodegenerative Diseases: Regulation of Cell Organelles Homeostasis

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Neurodegenerative diseases (NDDs) pose a significant public health challenge due to the rapid aging of the global population. Common features of NDDs include the abnormal aggregation of different proteins and disruption of normal function of organelles. Chaperone-mediated autophagy (CMA), one of the main pathways of lysosomal-mediated proteolysis, selectively delivers cytosolic proteins with an exposed KFERQ-like motif into the lysosomal lumen for degradation. CMA is essential for maintaining neuronal homeostasis, and its dysfunction has been implicated in aging and NDDs. Recent studies have revealed several mechanisms by which CMA is involved in the pathogenesis of NDDs. This review summarized the current understanding of the fundamental processes and regulatory mechanisms of CMA. Furthermore, we elucidate the links between CMA and NDDs, primarily focusing on how CMA regulates the function of cellular organelles in the pathological process underlying NDDs. Targeting impaired CMA represents an attractive and promising therapeutic strategy for the treatment of NDDs.

Keywords: neurodegenerative diseases (NDDs); chaperone-mediated autophagy (CMA); cell organelles; cell homeostasis

Introduction

Neurodegenerative diseases (NDDs) constitute a heterogeneous group of chronic diseases characterized by a gradual loss of selectively vulnerable populations of neurons. These include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), among others [1,2]. The global incidence of NDDs is rapidly increasing due to multifactorial etiologies, such as aging, genetic predisposition, and lifestyle. Despite extensive research, no effective therapeutics have been developed to decelerate, halt, or reverse the progression of NDDs [3,4]. Consequently, there is an urgent need to elucidate the underlying pathological mechanisms and develop more effective therapeutic strategies to combat these devastating diseases. Accumulating evidence suggests that organelle dysfunction plays a pivotal role in the pathogenesis of NDDs. Among the hallmarks of NDDs, deoxyribonucleic acid (DNA) and RNA defects and altered energy homeostasis can be considered the initiating triggers that drive the onset and progression of pathological processes [5–8]. These pathological hallmarks are intrinsically connected with organelle dysfunction, including the nucleus, mitochondria and others [9]. In certain NDDs, organelle dysfunction has been regarded as an early event and a central mechanism underlying neuronal loss, garnering extensive attention from researchers [10].

Proteostasis dysregulation, characterized by aberrant expression of mutant proteins or impaired degradation of damaged proteins leading to accumulation of protein aggregates, is a common feature of NDDs [9]. Eukaryotic cells have evolved various mechanisms to eliminate these aggregated proteins during evolution [11]. The autophagy-lysosome pathway (ALP), comprising macroautophagy (MA), microautophagy (MI), and chaperone-mediated autophagy (CMA), is a ubiquitous surveillance system that mediates the degradation of intracellular protein aggregates and damaged organelles across most cell types [12,13]. CMA is a unique intracellular protein degradation pathway found exclusively in mammalian cells, unlike MA and MI, which are conserved from yeast to mammals. The process of CMA does not involve the formation of vesicles, distinguishing it from other autophagic pathways. CMA is a highly selective intracellular protein degradation pathway that requires the assistance of chaperones to recognize and target proteins with a specific motif for degradation [14,15]. This selectivity allows for the removal of misfolded, damaged, or key signaling cytosolic proteins under various conditions, playing a critical role in protein quality control and maintaining cellular homeostasis. Studies have reported that CMA mediates the degradation of pathogenic proteins involved in NDDs, such as α-synuclein (α-syn) or tau protein. Failure of CMA has been implicated in the aggregation of these proteins during the progression of NDDs [16,17].

Recent studies have found that CMA also plays a crucial role in maintaining organelle homeostasis by degrading substrates that are master regulators of organelle function.

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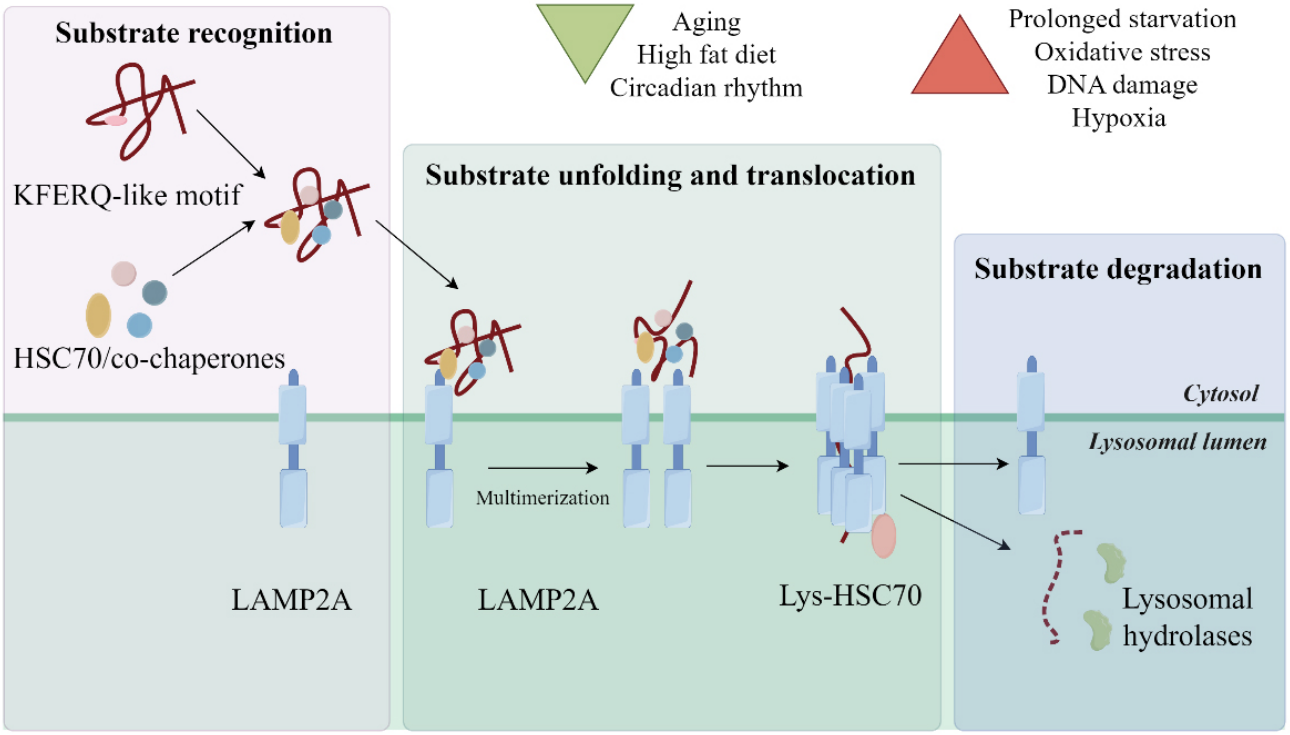

Fig. 1. The steps and regulators of CMA. There are three key elements (KFERQ-like motif, LAMP2A and HSC70) involved in CMA, and CMA is accomplished through successive steps, including substrate recognition, substrate unfolding and translocation, and substrate degradation. Top right: conditions that inhibit (green) or activate (red) CMA. The figure was created by the author using https://www.figdraw.com/. CMA, chaperone-mediated autophagy; HSC70, heat shock cognate protein 70 protein; LAMP2A, lysosome-associated membrane protein type 2A.

These substrates govern the fundamental compositions and biological processes of multiple organelles [18–20]. In this review, we summarize the recent findings regarding the relationship between CMA and several organelles and discuss the potential roles of CMA in the onset and treatment of NDDs.

Molecular Mechanisms of CMA

The process of CMA can be mainly divided into three distinct steps: (1) substrate recognition, where the chaperone heat shock cognate protein 70 (HSC70) recognizes and binds substrates containing KFERQ-like motif, forming an HSC70/substrate complex; (2) substrate unfolding and translocation, where the complex is transported to the lysosomal membrane surface, where it interacts with lysosome-associated membrane protein type 2A (LAMP2A), triggering the unfolding of the substrate and the assembly of LAMP2A into a multimeric complex; then, the unfolded substrate is translocated into the lysosomal lumen through a temporary channel formed by LAMP2A multimerization; and (3) substrate degradation, where the substrate is degraded by acid hydrolases in the lysosomal lumen [21]. Accordingly, there are three key elements in this process: KFERQ-like motif, LAMP2A, and HSC70 (Fig. 1).

KFERQ-like Motif

The recognition and selectivity of substrates for CMA are governed by the presence of a specific pentapeptide motif, termed the KFERQ-like motif, within the amino acid sequence of the target proteins. This motif, identified by the late American biochemist and cell biologist Fred Dice and his team during their study on the degradation of ribonuclease A, the first established CMA substrate, serves as a binding site for the molecular chaperone HSC70, facilitating the initiation of the CMA process [22–24]. Further research has found that the physical properties of the residues within the pentapeptide motif, rather than the specific amino acid sequence, determine the binding affinity of HSC70 to this region [25]. The motif consists of glutamine (at either end of the pentapeptide motif), one or two of the positive residues R and K, one of negative charged D or E residues and one or two of the hydrophobic residues (F, I, L, V).

In mammalian cells, approximately 40% of proteins in the cellular proteome contain a KFERQ-like motif [22,26,27], indicating a diverse array of substrates potentially regulated by CMA. In addition, post-translational modifications such as ubiquitin [27], phosphorylation [28,29] and acetylation [30] can alter the properties of amino acid residues,

generating canonical KFERQ-like motifs, greatly enhancing the flexibility of CMA and expanding the number of putative CMA substrates. For instance, in certain cases, phosphorylation of S/T/Y can confer properties akin to aspartic or glutamic acid, converting the protein into a CMA substrate. Acetylation of lysine residues in pyruvate kinase M1/2 (PKM2) can mimic the effect of a glutamine substitution. This modification generates a motif resembling the KFERQ sequence, promoting the degradation of PKM2 via CMA [31]. Post-translational modifications (PTMs), apart from introducing KFERQ-like motifs, can also modulate CMA substrates by facilitating conformational changes that either expose or mask the KFERQ-like motif. For example, acetylation of the mammalian Ste20-like kinase 1 (MST1) at a residue distant from its KFERQ-like motif prevents its CMA degradation by covering the motif. Only upon deacetylation can CMA degrade MST1 by binding the canonical motif [32]. In particular, a series of proteins associated with NDDs contain the KFERQ motif and are substrates for CMA [17,33]. For example, the accumulation of transactivation response DNA-binding protein 43 kDa (TDP-43) is a hallmark of amyotrophic lateral sclerosis (ALS). CMA can remove excess TDP-43 via HSC70, which binds to the KFERQ-like motif in TDP-43 [34]. Furthermore, α-synuclein, which deposits in the brains of PD patients, also contains a KFERQ-like motif, making it a canonical substrate for CMA degradation [35].

HSC70

HSC70, also known as HSPA8, is a multifunctional molecular chaperone involved in various cellular processes by facilitating the folding of unfolded or misfolded proteins in an adenosine diphosphate (ADP)/adenosine triphosphate (ATP)-dependent manner [31]. Notably, HSC70 can directly bind to the KFERQ-like motif in CMA substrates and deliver them to lysosomes for degradation. HSC70 contains three distinct domains: an amino-terminal adenosine triphosphatase (ATPase) domain, a substrate-binding domain, and a carboxyl-terminal domain. The conformational state of HSC70 is directly regulated by its nucleotide-binding state, with the ADP-bound form exhibiting a higher affinity for substrate binding compared to the ATP-bound form [36,37]. This process is modulated by co-chaperones like J-domain proteins (JDPs) and nucleotide exchange factors (NEFs), which associate ATP consumption and the ATPase cycle with conformational changes in HSC70, thereby influencing its substrate binding [38]. Post-translational modifications of HSC70 also affect its substrate binding. A recent study demonstrated that IKKα/β kinases can phosphorylate HSC70 at Ser85, located within the ATPase domain, stimulating its ATPase activity and inducing conformational changes that enhance substrate affinity. This finding provides evidence that protein kinase can directly phosphorylate and regulate HSC70 activity, implicating its contribution to CMA [39].

In addition to the cytosolic pool, a portion of HSC70 is present in the lysosomal lumen and associated with the lysosomal membrane on the cytosolic side, playing critical roles in the CMA process and being indispensable for this degradative pathway [40,41]. The lysosomal membrane-associated HSC70 forms a complex with other cochaperones (i.e., HSP90, HSP40, HSP70-interacting protein HIP) that participates in substrate unfolding before lysosomal translocation and promotes the dissociation of the oligomeric LAMP2A complex to allow the subsequent binding of new substrate [42]. The luminal form of lysosomal HSC70 is necessary for completing substrate translocation into lysosomes and serves as an indicator of CMA-competent lysosomes. In contrast to the neutral isoelectric point of cytosolic HSC70, the luminal HSC70 has a highly acidic isoelectric point and becomes unstable with small increases in lysosomal pH [43]. The mechanism by which HSC70 gains access to the lysosomal lumen is not well understood. Apart from its role in CMA, HSC70 has been shown to actively regulate MA and endosomal-microautophagy (eMI). Notably, HSC70 is highly expressed in the mammalian nervous system, particularly in neuronal cell bodies [44]. The relationship between HSC70 and NDDs has been well-established. Ongoing studies continue to refine and expand our comprehension of HSC70's complex biological roles in NDDs, including HSC70-mediated protein degradation and its anti-apoptotic role in neuroprotection [45].

LAMP2A

As the CMA receptor, LAMP2A interacts with the HSC70/substrate complex and mediates the translocation of substrate to the lysosomal lumen. LAMP2A is one of the three isoforms (LAMP2A, 2B, 2C) generated by alternative splicing of *LAMP2* and is the only variant required for CMA, thus acting as the rate-limiting factor of CMA [46–48]. Structurally, LAMP2A consists of a highly glycosylated lumen domain, a single transmembrane domain, and a short cytosolic tail containing positively charged residues that bind to the HSC70/substrate complex [49]. Upon interacting with the HSC70/substrate complex, monomeric LAMP2A multimerizes to form a translocation complex across the lysosomal membrane, enabling the substrate to be internalized into the lysosome. After that, LAMP2A in the multimeric complex dissociates into monomers with the assistance of lysosomal Hsc70 [21]. Decreased protein levels of LAMP2A are intimately associated with the occurrence and development of NDDs. In the *Drosophila* brain, LAMP2A promotes autophagic flux and prevents α-synuclein-induced PD-like symptoms [13]. In *LAMP2A* knockout mouse models, it has been linked with the pathogenesis of different NDDs [50]. Moreover, the reduction of LAMP2A levels is found in the substantia nigra pars compacta (SNc) region of PD patients [51,52].

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The activity of CMA is tightly associated with the protein level of LAMP2A on the lysosomal membrane, which represents a convergent point for multiple signaling pathways [47,53]. Prolonged starvation prevents the cleavage of LAMP2A by cathepsin A within the lipid microdomains of the lysosomal membrane, thus increasing the stability of this protein and inducing CMA activation. Conversely, aging or a high-fat diet leads to an expansion of lipid microdomains, accelerating the degradation of LAMP2A, which compromises the CMA flux. Other stress conditions, such as oxidative stress, hypoxia, and DNA damage have been reported to augment CMA activity by upregulating the transcription and synthesis of LAMP2A. This upregulation is mediated by the nuclear factor of activated T cells (NFAT1) and other potential transcriptional factors yet to be identified [21]. At the translational level, microRNAs (miRNAs) have been identified to interact with either LAMP2A or HSC70, reducing the levels of these proteins in PD patients [52]. A recent study has linked CMA activity with the circadian rhythm. CMA activity is temporally regulated by the circadian rhythm through cyclic repression of LAMP2A. Notably, the circadian properties of CMA are tissue- and cell-type-dependent [54].

Roles of CMA in Organelles Homeostasis in NDDs

CMA was initially hypothesized to participate in amino acid recycling [55], potentially enhancing cell survival during prolonged starvation by degrading non-essential proteins while maintaining essential ones [56]. Furthermore, CMA functions as a protein quality control mechanism by selectively removing misfolded or damaged proteins, thus maintaining proteostasis under various stress conditions. For example, under oxidative stress caused by toxic compounds, CMA activity is upregulated to timely degrade oxidatively damaged proteins [57]. Inhibition of CMA significantly exacerbates the buildup of oxidized proteins, while concurrently reducing cell viability [58]. In addition, by selectively recognizing and degrading a variety of signaling proteins, CMA precisely regulates key pathways involved in cellular metabolism, differentiation, immune response, DNA damage response, and cellular senescence [16,59–61]. Recent evidence suggests that CMA plays a vital role in modulating the function of cellular organelles, exerting pro-survival effects in neurons [62,63]. Disturbance of these processes may contribute to the pathogenesis of neurodegeneration.

Extensive fundamental and clinical research spanning several decades has elucidated eight distinct hallmarks associated with neurodegeneration, including DNA and RNA defects, altered energy metabolism, pathological protein aggregation, aberrant proteostasis, synaptic and neuronal network dysfunction, cytoskeletal abnormalities, inflammation, and neuronal cell death [9]. Especially, some of them are related to organelles dysfunction (Fig. 2). Nuclear dysfunction in neurodegeneration, including DNA defects, telomere attrition, and epigenetic alterations, is regarded as an initial risk factor for most NDDs [64]. Disruption in mitochondrial function and metabolism occurs early in the pathogenesis of several NDDs [6,65], which has become an important field of NDD research in recent years. As the quality-control organelle for protein homeostasis, the endoplasmic reticulum (ER) and Golgi apparatus dysfunction are associated with the accumulation of toxic protein in NDDs [66,67]. The functional links between these organelles and the CMA pathway highlight the core role of CMA in regulating organelle function in NDDs (Fig. 3).

Regulation of the Nucleus

The nucleus is the largest organelle in eukaryotic cells, serving as the control center and playing a crucial role in various cellular processes. It functions as the storage site for the genetic material, deoxyribonucleic acid (DNA), as well as the primary location where DNA replication and transcription occur. In addition to DNA, the nucleus harbors a diverse array of components, including heterogeneous nuclear ribonucleoproteins (hnRNPs), ribosomal RNA (rRNA), and proteins such as transcriptional factors and DNA damage response molecules. These components within the nucleus cooperatively work together to sustain nuclear homeostasis. Any dysregulation or disruption of this interplay can lead to impaired nuclear function, potentially contributing to NDDs [68]. For example, heterogeneous nuclear ribonucleoproteins (hnRNAs) assist in controlling the maturation of newly synthesized pre-messenger RNAs (pre-mRNAs) into messenger RNAs (mRNAs) and stabilizing mRNAs during their intracellular transport [69]. Perturbations in hnRNA function have been implicated in the pathogenesis of multiple neurological diseases, such as spinal muscular atrophy (SMA), ALS, and AD [70]. Additionally, several studies have demonstrated that disruptions in the subcellular localization of nuclear transcription factors are observed in affected neurons in NDDs [71,72]. Defects in the cellular response to single-strand or double-strand breaks in DNA underpin many human NDDs. Efficient DNA damage repair mechanisms are essential for maintaining genomic stability and have been shown to be protective in NDDs [73]. Interestingly, CMA has been demonstrated to play an important role in NDDs by modulating various processes within the cell nucleus, including transcriptional regulation and genome quality control. The following points will be discussed in detail.

Transcriptional Regulation

Transcriptional factors play a crucial role in determining the fate of various cell types, including neuron and glial cells. A tightly controlled protein level of activity of transcriptional factors is essential to prevent neu-

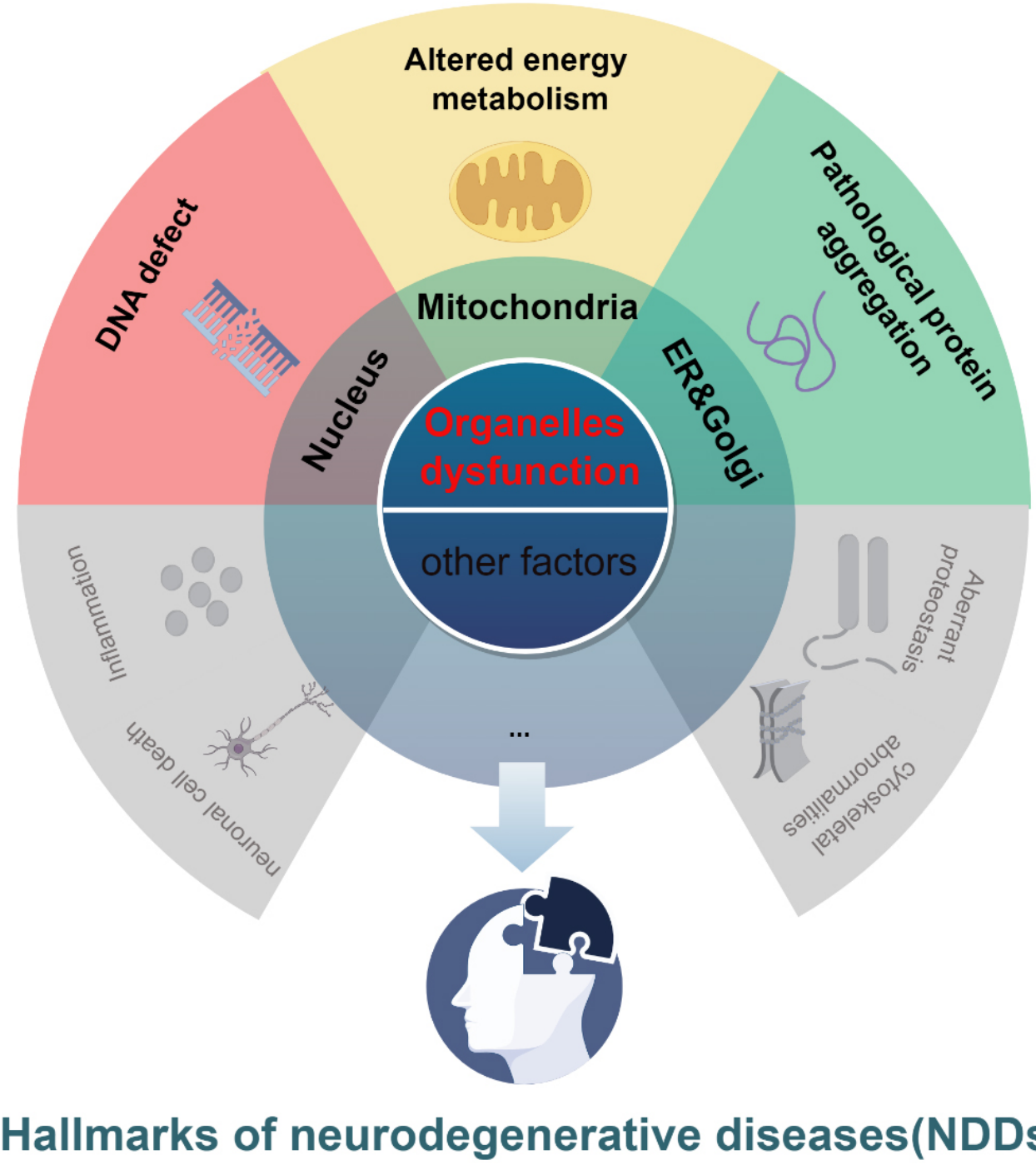

Fig. 2. The relationship between organelle dysfunction and NDDs. Organelles (nucleus, mitochondrial, ER, and Golgi) dysfunction is tightly related to the hallmarks of neurodegeneration, including DNA defect, altered energy metabolism, and pathological protein aggregation, which are considered the most important risk factors for NDDs. This figure was created by the author using https://www.figdraw.com/. NDD, neurodegenerative diseases; ER, endoplasmic reticulum.

ronal degeneration under various stress conditions. Recent studies have implicated CMA in the regulation of nuclear transcriptional factor degradation, and disruption of this modulatory mechanism may promote the development of NDDs [74,75]. One example is the neuronal growth factor myocyte enhancer factor 2D (MEF2D), which has been demonstrated to be a substrate of CMA in dopaminergic (DA) neurons [58,61]. Physiologically, MEF2D interacts with HSC70, facilitating its continuous shuttling from the nucleus to the cytoplasm for lysosomal degradation via CMA. However, aberrant accumulation of α-synuclein or expression of the PD-associated A53T α-synuclein mutant

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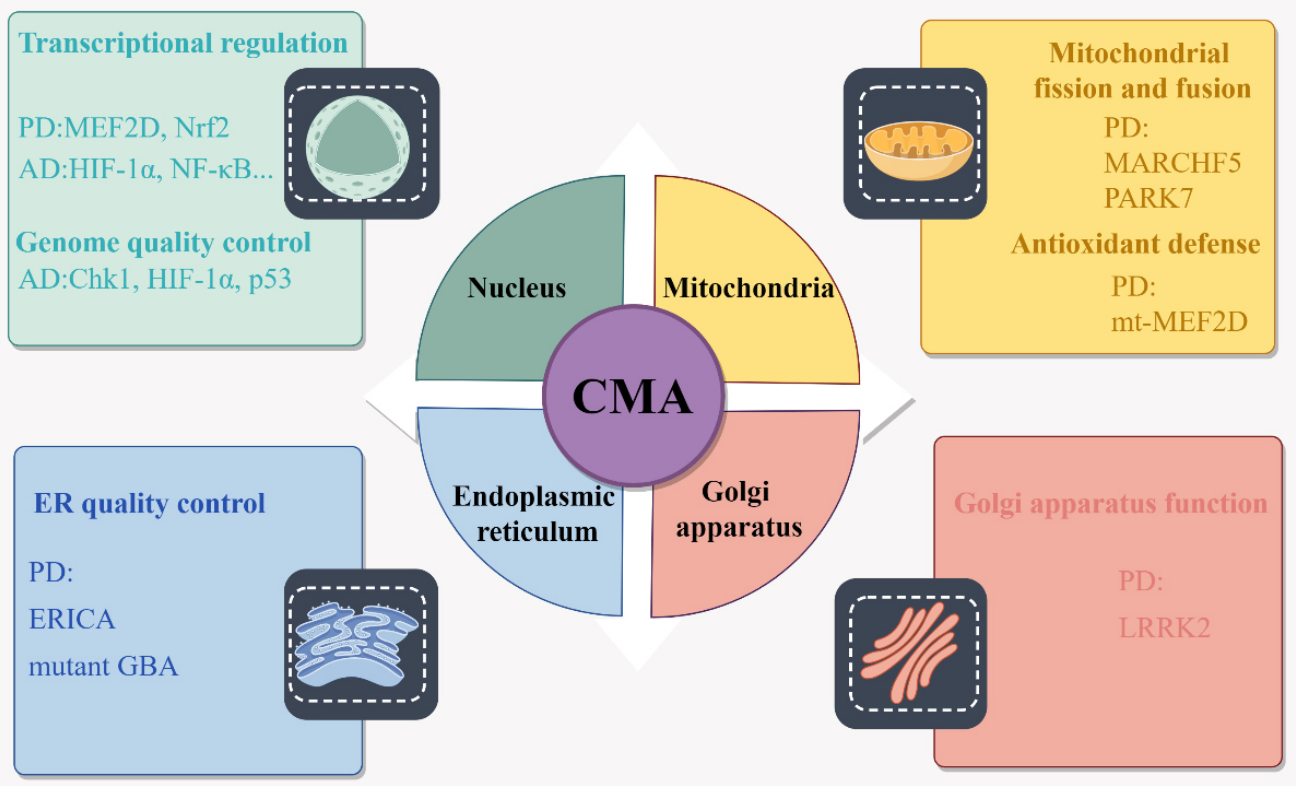

Fig. 3. Roles of CMA in organelles homeostasis in NDDs. CMA is engaged in regulating the function of organelles by degrading key signaling substrates or components related to organelle homeostasis and the dysfunction of this regulatory pattern will contribute to the pathology of NDDs. The figure was created by the author using https://www.figdraw.com/. PD, Parkinson's disease; AD, Alzheimer's disease; MEF2D, myocyte enhancer factor 2D; Nrf2, Nuclear factor erythroid 2-related factor 2; HIF-1α, hypoxia-inducible factor-1α; NF-κB, nuclear factor-κB; Chk1, checkpoint kinase 1; p53, a 53-kDa nuclear protein; MARCHF5, membrane associated ring-CH-type finger 5; PARK7, Parkinson disease 7; mt-MEF2D, mitochondrial MEF2D; ERICA, ER stress-Induced Chaperone-mediated Autophagy; GBA, glucocerebrosidase; LRRK2, leucine rich repeat kinase 2.

in DA neurons disrupts the binding between MEF2D and HSC70, leading to cytoplasmic accumulation of inactive MEF2D and increases the neuronal vulnerability to stress. Consistent with this, the level of MEF2D in the cytoplasm was significantly higher in the brains of A53T transgenic mice and PD patients compared to the control group. Nuclear factor erythroid 2-related factor 2 (Nrf2), a member of the Cap'n'Collar-basic leucine zipper (CNC-bZIP) transcription factors, preferentially binds to the cis-acting antioxidant responsive element and launches an adaptive response aimed at reversing redox imbalance upon oxidative stress [76,77]. The major survival role of Nrf2 has been widely studied [78]. A recent study demonstrated that CMA directly degraded Kelch-like ECH-associated protein 1 (Keap1), an adaptor of the E3 ligase complex interacting with Nrf2 and regulating its ubiquitination, thus facilitating the degradation of Nrf2 [79,80]. Prolonged oxidative stress activates the CMA pathway, which leads to an increase in the levels of the transcription factor Nrf2. This occurs through the timely removal of Keap1, inducing the expression of multiple downstream antioxidative genes and rendering DA neurons the ability to resist oxidative damage induced by varying doses of 6-hydroxydopamine (6-OHDA). Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that mediates a broad repertoire of adaptive responses to hypoxia. Specifically, it has been shown that HIF-1α deficiency aggravates the pathology and accelerates the progression of NDDs [81,82]. For instance, emerging evidence has revealed that HIF-1α transcriptionally upregulates BACE1 and non-transcriptionally activates γ-secretase, thereby promoting amyloid-beta (Aβ) production under hypoxic-ischemic conditions and contributing to the development of AD [83]. Notably, lysosomal degradation of HIF-1α by CMA is a major regulator of nuclear HIF-1 activity [75]. Nuclear factor-κB (NF-κB), a well-established transcription factor implicated in neuroinflammatory processes in NDDs, is also regulated by CMA through the degradation of its inhibitor, NF-κB inhibitor-α (IκBα), during starvation [84]. The functional consequences of the CMA-HIF-1α/NF-κB axis in NDDs are issues worthy of study. Notably, proteome-wide analysis of CMA targeting motifs unravels that additional transcription factors involved in various aspects of cellular homeostasis are potential substrates of CMA, indicating a broader reg-

ulatory role of CMA in nuclear transcription [27]. However, whether these transcription factors are authentically degraded by CMA and their specific roles in NDDs remain largely unexplored and require further investigation.

Genome Quality Control

The accumulation of DNA damage is a common feature shared by many NDDs [85,86]. Cells have evolved multiple mechanisms to detect and repair various types of DNA damage caused by environmental stress or replicational errors, including direct repair, base excision repair, nucleotide excision repair, double-strand break repair, and cross-link repair [87]. Recent studies have implicated that CMA acts as a key component of the guardian system to maintain genomic integrity by regulating the degradation of activated checkpoint kinase 1 (Chk1, also known as phosphorylated serine/threonine-protein kinase) after genotoxic insult [18,74]. In the absence of CMA, nuclear accumulation of Chk1 leads to hyperphosphorylation and destabilization of the Mre11-Rad50-Nbs1 (MRN) complex, which participates in the early steps of DNA repair pathways. This compromises cell cycle progression and prolongs the time that DNA damage persists [18]. The HIF-1α subunit works as a negative regulator of DNA replication, in addition to its classical role as a transcriptional factor. This is partly mediated through its binding to the minichromosome maintenance proteins, which are essential DNA replication factors crucial for helicase activation and initiation of DNA synthesis during the cell cycle. The inhibition of CMA results in HIF-1α-dependent cell-cycle arrest [21,88]. Additionally, p53, a 53-kDa nuclear protein, has emerged as a crucial molecule in NDDs, beyond its significance in cancer research [89]. As a "genome guardian", p53 is activated in response to DNA damage to prevent gene amplification and facilitate timely repair [90]. Primarily, p53 induces cell death, thereby promoting NDD pathology by inducing cell cycle arrest and cellular senescence [91,92]. Furthermore, p53 activation triggers the generation of reactive oxygen species (ROS), expression of pro-inflammatory genes, and aggregation of pathological proteins, which further contribute to the progression of NDDs [92–94]. A recent study demonstrated that CMA downregulates p53 levels and activity by degrading its upstream regulator high-mobility group box 1 (HMGB1) [95]. However, another study suggested that CMA maintains the guarding function of p53 on DNA by efficiently removing mutant p53 variants that interfere with the wild-type protein [96]. Altogether, these findings highlight the intricate role of CMA in modulating nuclear processes, including nuclear transcriptional activity and genetic stability.

Regulation of Mitochondria

Mitochondria are membrane-bound organelles and the energy center of the cell by generating large quantities of ATP. In addition, mitochondria are also involved in other cellular processes, such as inflammation, calcium storage, and cell death signaling [97,98]. Neurons are post-mitotic and high energy-consuming cells due to intrinsic characteristics, which makes them more susceptible to mitochondrial dysfunction, compared to other types of cells. Accumulating evidence strongly implicates mitochondrial dysfunction as a pathogenic factor in the development of NDDs [99,100]. Chronic mitochondrial dysfunction leads to impaired ATP generation and provokes the accumulation of reactive oxygen species (ROS), which was found in patients diagnosed with NDDs [100]. Besides, recent research has verified that the leakage of mitochondrial DNA (mtDNA) into the cytosol can elicit an innate immune response in neuronal cells. This response can give rise to persistent neuroinflammation, which has been causally linked to the progression of NDDs [101]. Notably, several genetic factors associated with NDDs, such as mutations in the *Pakin* and *PINK1* genes, are known to converge their pathogenic effect primarily on mitochondrial function [102,103]. Given the critical role of mitochondrial dysfunction in NDDs and the susceptibility of mitochondria to damage, mitochondrial quality control (MQC) mechanisms that ensure proper functionality of this organelle are particularly important in neurons. MQC involves multiple processes, including mitochondria biogenesis, mitochondrial fission and fusion, elimination of damaged mitochondria, antioxidant defense and mtDNA repair [104]. The autophagy-lysosome pathway (ALP) is known to actively modulate MQC by removing abnormal mitochondria via mitophagy, a selective form of macroautophagy. Recent findings have revealed that CMA also participates in MQC, extending our knowledge about the role of ALP in maintaining MQC [19,105].

Mitochondrial Fission and Fusion

Mitochondria are highly dynamic organelles that constantly change their morphology to permit efficient adaptation to the changing demands of cells, a process achieved via mitochondrial fission and fusion. Maintaining a balance between fission and fusion is indispensable for sustaining a normal mitochondrial network. Excessive fission leads to fragmented and dysfunctional mitochondria, which is an important pathological feature in multiple NDDs. In mammals, fusion is controlled by the dynamin-related GTPase mitofusin 1 (MFN1) and mitofusin 2 (MFN2) located at the outer mitochondria membrane and OPA1 (OPA1 mitochondrial dynamin-like GTPase) at the inner mitochondria membrane. Mitochondrial fission is regulated by the cytosolic protein dynamin-related protein 1 (Drp1), which translocates to mitochondria under stress conditions. Drp1 is subject to different post-translational modifications,

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including phosphorylation, S-nitrosylation, ubiquitination, and O-GlcNAcylation, depending on the cellular environment [106]. Particularly, its ubiquitination mediated by E3 ubiquitin ligase membrane-associated ring-CH-type finger 5 (MARCHF5) regulates the mitochondrial translocation of Drp1, thereby modifying mitochondrial morphology [107,108]. A recent study demonstrated that MARCHF5 is a bona fide substrate for CMA. CMA inhibits the translocation of Drp1 to mitochondria and subsequent mitochondrial fission by degrading MARCHF5 under oxidative stress. Enhanced CMA by LAMP2A overexpression inhibits excessive mitochondrial fission and DA neuron death in the PD mouse model [19]. Parkinson's disease 7 (*PARK7*), also known as *DJ-1*, encodes a ubiquitous, highly conserved protein, which is closely related to the regulation of mitochondrial function and morphology [109]. Mutation of the *DJ-1* gene leads to mitochondrial defects and is associated with autosomal recessive early-onset parkinsonism [110]. Interestingly, oxidatively damaged DJ-1 is a direct CMA substrate [111]. In this context, CMA protects cells against neurotoxin-induced mitochondrial damage by timely degradation of oxidized DJ-1, which becomes non-functional and interferes with the normal function of its counterpart. These identifications highlight and strengthen the critical role of CMA in mitochondrial dynamics in NDDs.

Antioxidant Defense

The overproduction of ROS is a primary manifestation of mitochondrial dysfunction. Oxidative phosphorylation in mitochondria, facilitated by the electron transport complex (ETC), is the main source of cellular ROS [112,113]. Physiological levels of ROS, including peroxides, superoxides, and hydroxyl radicals, play a crucial role in regulating intercellular signal transduction pathways that affect cell proliferation, differentiation, and apoptosis [114]. However, excessive ROS production resulting from dysfunctional mitochondria is toxic and evokes oxidative stress, which contributes to cell death in NDDs [115,116]. A series of studies demonstrated that CMA can be significantly activated by ROS to increase the lysosomal-mediated uptake and degradation of oxidatively damaged proteins [57,117]. Moreover, CMA can also promote the elimination of ROS by facilitating the expression of antioxidative genes through enhancing the transcriptional activity of Nrf2 as mentioned above [19,111]. Decreased activity of the ETC has been implicated in the generation of oxidative stress and has been evidenced in the substantia nigra (SN) of sporadic PD patients [118]. In addition to its role as a nuclear transcription factor, MEF2D in DA neuron is also present in mitochondria, where it binds to the coding region of mitochondrial DNA (mtDNA) to control the expression of NADH dehydrogenase 6 (ND6), an essential component of the complex I of ETC [119,120]. Genetic ablation of *MEF2D* leads to impaired complex I activity, reduced ATP levels, and increased hydrogen peroxide formation. Moreover, the expression levels of mitochondrial MEF2D and ND6 were greatly lessened in the midbrains of both MPTP-treated mice and human PD patients [113,119]. Since CMA inhibition leads to the weakened transcriptional activity of MEF2D, the CMA-MEF2D axis may represent an effective defense mechanism to maintain mitochondrial homeostasis upon oxidative stress [20].

Regulation of Endoplasmic Reticulum

The endoplasmic reticulum (ER) is a large organelle spread throughout the cytoplasm, specialized in folding, modification, and assembly of newly synthesized proteins, lipid synthesis, and calcium storage [121,122]. The structure and function of ER are extremely sensitive to changes in the cellular environment. ER disturbance can lead to an undermined capacity for protein folding. In such instances, the misfolded or unfolded proteins are subjected to ubiquitination and translocated to the cytosol to be degraded by the proteasome pathway. This process is known as ER-associated degradation (ERAD) [123,124]. If ER is incompetent to cope with the excess of unfolded or misfolded proteins, it leads to ER stress, which activates the PERK/eIF2α/ATF4, IRE1/XBP1, and ATF6 signaling pathways, collectively termed as the unfolded protein response (UPR). While the UPR initially serves as an adaptive mechanism to restore ER homeostasis and promote cell survival, prolonged and unresolved ER stress can ultimately activate apoptotic pathways, resulting in abnormal neuronal death in several NDDs, such as AD, PD, ALS, and Prion diseases [125–128]. Numerous studies have shown that ER stress can induce MA to degrade ubiquitinated proteins or part of the ER compartments (known as ER-phagy) to restrain ER stress [129–131]. The relationship between ER stress and CMA was elucidated in a recent study which revealed that p38 MAPK can sense and transmit ER stress to the lysosome, thereby activating CMA via phosphorylation of LAMP2A [53]. Mechanistically, ER stress leads to PERK-dependent activation and recruitment of MKK4 to the lysosomes, where it activates the lysosomal pool of p38 MAPK. The lysosomal p38 MAPK directly phosphorylates the CMA receptor LAMP2A at threonine 211 (T211) and threonine T213 (T213). This dual phosphorylation modification increases the stability of LAMP2A, promotes its oligomerization and conformational change on the lysosomal membrane, and subsequently activates CMA, which couples between ER stress and CMA and is termed as ER stress-Induced Chaperone-mediated Autophagy (ERICA) [63]. ERICA is essential for maintaining cellular homeostasis. Uncoupling ERICA sensitizes cells to ER stress-induced death and results in a greater loss of SNc DA neurons in a PD mouse model. This highlights the importance of CMA in mitigating ER stress and preventing neuronal death [60]. Furthermore, studies on glucocerebrosidase (GBA), a lysosomal enzyme synthesized in the ER, provide

additional evidence for the role of CMA in ER quality control. In PD, heterozygous mutant alleles of the *GBA* gene encode disease-associated GBA forms that fail to properly fold in the ER. These unfolded mutant GBA proteins are recognized by the cytosolic chaperone HSC70 and targeted for degradation by CMA [132]. Together, these findings point out a previously unrecognized role for CMA in ER quality control in NDDs.

Regulation of Golgi Apparatus

The Golgi apparatus is a cluster of membrane-bound compartments that plays a crucial role in intracellular membrane trafficking and protein sorting in all eukaryotic cells. It also participates in modifying proteins transported from the ER through various post-translational modifications, including glycosylation, sulfation, and phosphorylation. It is estimated that more than 30% of the proteins encoded in the human genome transit through the Golgi apparatus, involving multiple cellular processes such as autophagy, DNA repair, innate immunity, and pro-inflammatory responses [133–137]. Consequently, the Golgi apparatus actively participates in maintaining cell homeostasis. Golgi apparatus fragmentation and dysfunction have been observed as an early pathological feature that preceded other alterations in some NDDs [138–140]. For instance, neurons displaying neurofibrillary tangles (NFT) in AD tend to contain more disrupted Golgi apparatus, which is evidenced by quantitative analysis showing reduced surface area and volume of the Golgi apparatus in temporal and hippocampal pyramidal neurons of AD patients [141]. In PD animal models, an overabundance of α-synuclein in nigral DA neurons leads to extensive Golgi apparatus fragmentation [142]. Therefore, maintenance of the function of the Golgi apparatus is considered a potential therapeutic target for NDDs. In recent years, a growing body of research has demonstrated that damaged Golgi apparatus can be degraded by lysosomes through a selective form of MA in response to cellular stress inside and outside the cell, which is termed as Golgiphagy [143,144]. In addition to MA, accumulating evidence suggests an intimate relationship between CMA and Golgi quality control [145–147]. Notably, the protein levels of LAMP2A in the lysosome membrane are tightly regulated by the Golgi apparatus [148]. Newly synthesized LAMP2A is glycosylated in the Golgi apparatus and sorted by the mannose-6-phosphate (M6P) receptor to reach the lysosome. Concurrently, the stability of LAMP2A is modulated by the endosome-Golgi retrieval of membrane proteins. Mutations in the vacuolar protein sorting 35 (*VPS35*) gene, associated with autosomal dominant PD, disrupt the cycling of LAMP2A and accelerate its degradation, contributing to impaired CMA activity in PD [148]. Furthermore, recent studies have revealed that certain regulators of the Golgi apparatus are CMA substrates [149]. One example is the leucine-rich repeat kinase 2 (*LRRK2*) whose mutations are currently recognized to be the most common genetic cause of familial PD and contribute to sporadic PD as well. WT LRRK2 is degraded via CMA, whereas its pathogenic mutated counterparts exhibit resistance to this degradative pathway [149,150]. Notably, a portion of LRRK2 localizes to the Golgi apparatus and affects its integrity and vesicle trafficking by interacting with functional regulators of this organelle, such as VPS52, ArfGAP1, and NSF [151–153]. The accumulation of mutated LRRK2 disrupts the normal functioning of the Golgi apparatus, consequently impairing numerous neuronal processes like neurite outgrowth. Further investigations are warranted to elucidate the precise pathological role of the CMA-LRRK2 axis in Golgi apparatus dysfunction and to determine whether other Golgi apparatus-related modulators are substrates of CMA.

Future Challenge and Therapeutic Strategies

While approximately 40% of cytosolic proteins possess the KFERQ-like motif in their sequence, our understanding of the CMA's ability to regulate organelles beyond those mentioned in this review by modulating the stability of specific substrates remains limited. This presents the possibility of extending the functionality of CMA. In particular, neurons are highly specialized cells with complex morphology and functions. However, our understanding of neuron-specific CMA functions is still relatively limited. Apart from regulating neuronal survival by removing non-functional neuronal survival factor MEF2D and neurotoxic proteins (a-syn, tau, LRRK2, etc.) that we have discussed above, a recent study showed that CMA in neuron dendrites enabled local disposal of aggregation-prone proteins through lysosomal exocytosis, thus modulating the growth of dendritic spines [154]. This finding shed light on the neuron-specific CMA functions. Another study revealed that loss of CMA activity in excitatory neurons alters neuronal function, induces proteotoxicity, and selectively impacts the neuronal metastable proteome involved in glycolysis and calcium metabolism. Notably, the absence of compensatory activation of macroautophagy upon CMA blockage in excitatory neurons highlights the specific effect of CMA on neuronal function [17,155]. The emergence of novel techniques like fluorescence lifetime imaging and proteome-wide analysis will enable the identification of additional substrates and functionality of CMA. Several questions require further investigation and understanding. Which type of substrate and under which condition will CMA degrade the protein? Does it degrade the target functional proteins containing the KFERQ motif for removal to regulate the function of organelles, apart from mostly misfolded proteins? The existence of crosstalk between CMA and other proteolytic pathways in regulating organelle function is an intriguing question, given that many proteins can be degraded by multiple degradative

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pathways. For instance, propionylation can shift the degradation of HIF-1α from the UPS to CMA. However, the underlying mechanisms mediating the 'crosstalk' among these pathways remain to be elucidated [156]. Notably, the activity of CMA appears to be differentially modulated in various cell types or distinct stages of NDDs, suggesting that the regulatory effect of CMA on organelle function may be time and spatial-specific [157]. These challenges remain to be addressed before efficient strategies based on CMA can be developed for the treatment of NDDs. Nonetheless, preliminary drug development and biotechnological applications targeting CMA for NDD treatment are progressing steadily. The KFERQ-like motif facilitates the recognition of specific substrates by CMA. A novel lysosome targeting chimera has been recently developed. This chimera, termed split-and-mix chaperone-mediated autophagy-based degrader (SM-CMAD), conjugates the KFERQ-like motif with the Phg-Phg-Arg-Arg tetrapeptide core motif via chemical bonds [158]. This strategy could be utilized to remove cytosolic proteins once they are fused with the SM-CMAD tag. This approach provides an intriguing framework for the subsequent development of CMA-based protein degraders in NDDs. Alternatively, certain small molecules have been found to improve NDDs by activating the CMA pathway [159]. Metformin can induce CMA augmentation through stimulation of the TAK1-IKKα/β-phosphorylation HSC70 Ser85 signaling axis, thereby facilitating the CMA-mediated clearance of toxic amyloid precursor protein (APP) and Aβ, ultimately reversing both the molecular and behavioral characteristics associated with AD [39]. The retinoic acid receptor alpha (RARα) antagonists exhibit potential therapeutic efficacy through the activation of CMA in a PD mouse model [160]. A recent study found that chemical activation of CMA by a novel compound, CMA activator 77.1 (CA77.1), ameliorates the pathological features in AD mouse models [17]. Although these therapeutic outcomes are in the early stages, they instill considerable confidence in the future potential of targeting CMA for treating NDDs.

Conclusions

CMA is an essential proteolytic pathway characterized by the direct translocation of selective substrates across the lysosomal membrane, which is indispensable for sustaining cellular homeostasis, especially in neurons. Compared to nearly 30 years ago when the process of lysosomal-mediated selective degradation of KFERQ motif-containing protein, later named CMA, was first reported, significant progress has been made in CMA-related research over the past decades. Particularly, CMA has garnered considerable attention in the field of NDDs research, based on the well-established observation that CMA activity declines with aging and is further diminished in the brains of individuals diagnosed with NDDs. In addition to its established function in removing non-essential proteins and oxidatively damaged proteins to preserve the viability of cells under stress conditions, CMA is also involved in regulating the function of cellular organelles by degrading key signaling substrates related to organelle homeostasis. These studies broaden our understanding of how impaired CMA contributes to the pathogenesis of NDDs. Furthermore, they provide compelling evidence supporting further investigation of CMA as a potential therapeutic strategy for treating NDDs.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

XBL and JJL: contributed to the concept and designed the research study and wrote the paper. TJN, CJS and QY designed the work and revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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