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EDITED BY
Jun Zhao,
United States Food and Drug Administration, United States

REVIEWED BY
Liming Wang,
Hunan University, China
Kaige Yan,
Southern University of Science and Technology, China

*CORRESPONDENCE
Hanting Yang
yanght@fudan.edu.cn
Hao Zhang
hao_zhang@fudan.edu.cn

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Mitochondrial quality control in the brain: The physiological and pathological roles

Xurui Shen, Peixin Sun, Hao Zhang* and Hanting Yang*

Institute for Translational Brain Research, State Key Laboratory of Medical Neurobiology, MOE Frontiers Center for Brain Science, Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China

The human brain has high energetic expenses and consumes over 20% of total oxygen metabolism. Abnormal brain energy homeostasis leads to various brain diseases. Among multiple factors that contribute to these diseases, mitochondrial dysfunction is one of the most common causes. Maintenance of mitochondrial integrity and functionality is of pivotal importance to brain energy generation. Mitochondrial quality control (MQC), employing the coordination of multiple mechanisms, is evolved to overcome many mitochondrial defects. Thus, not surprisingly, aberrant mitochondrial quality control results in a wide range of brain disorders. Targeting MQC to preserve and restore mitochondrial function has emerged as a promising therapeutic strategy for the prevention and treatment of brain diseases. Here, we set out to summarize the current understanding of mitochondrial quality control in brain homeostasis. We also evaluate potential pharmaceutically and clinically relevant targets in MQC-associated brain disorders.

KEYWORDS

mitochondrial quality control, mitochondrial dysfunction, brain disorders, mitochondrial homeostasis, therapeutic target

Introduction

The brain is the most important and intricate component of the central nervous system (CNS). In addition to controlling how the body moves, it regulates higher neural activities including spirit, language, learning, memory, and consciousness. Brain damage causes reduced body function, such as memory loss, cognitive impairment, sensory deficits, and behavioral abnormalities. Brain disorders, from neurodegenerative to psychiatric illnesses, have drawn increasing attention in recent years (VanItallie, 2019; Xie et al., 2019; Oh et al., 2021; Wang et al., 2021).

In humans, the brain accounts for approximately 2% of the body weight, while it consumes over 20% of the body's energy needs (Ambekar et al., 2021). It is well-known that mitochondria are the center of energy metabolism. They are essential for brain metabolism, development, and function. Although a variety of factors contribute to brain disorders, evidence postulates that mitochondrial dysfunction is one of the leading causes (Guntuku et al., 2016; Lan et al., 2022). Unhealthy and aged brains often show aberrant mitochondrial structures and excessive reactive oxygen species (ROS), which is related to many adult-onset brain diseases, ranging from injuries and infections to brain tumors and dementia (**Figure 1**; Sultana et al., 2011; Chouchani et al., 2014; Zorov et al., 2014; Cheng et al., 2020; Iranmanesh et al., 2021). Accordingly, the maintenance of mitochondrial homeostasis is crucial for brain function. Cell employed numerous strategies to coordinate protein and organellar quality control, including mechanisms to monitor the mitochondria. In this review, we discuss the pathways of mitochondrial quality control (MQC) and its role in the progression of brain diseases, and briefly summarized the known MQC-related potential drug targets.

Physiological functions of mitochondria in the brain

ATP production, metabolism, and oxidative phosphorylation

Mitochondria participate in energy and free radicals production, cell metabolism, cell death, and inflammation in the brain (Martin, 2010; Yin et al., 2016; Stefanatos and Sanz, 2018; Bader and Winklhofer, 2020). Mitochondria are the primary sites of ATP production as well as catabolic biochemical processes such as glycolysis, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation (OXPHOS). At synapses, neurons in the brain exchange chemical and electrical signals with one another. Maintaining electrochemical gradients, liberating and recycling synaptic vesicles, and other very energy-intensive procedures rely on mitochondrial ATP synthesis (Devine and Kittler, 2018). It has been predicted that axonal terminals consume 4.5×10^8 ATP during an action potential (and downstream synaptic events), compared to 3×10^6 ATP used by resting potentials and housekeeping (Harris et al., 2012). The ATP-dependent membrane pumps, such as Na^+/K^+ ATPase and Ca^{2+} ATPase, are powered by about 55% of the total ATP produced by neurons in order to maintain the resting potential by resetting ionic gradients (Harris and Attwell, 2012). In addition, synaptic vesicle recycling also consumes a significant amount of energy. Each glutamate synaptic vesicle recycling event requires more than 2×10^4 ATP molecules, and in order to restore ionic gradients at a steady state, 1×10^6 ATP molecules must be restored within each individual neuron terminal (Rangaraju et al., 2014). Besides that, the process of cargo transportation along axons, which is carried out by motors, kinesins, and cytoplasmic dynein, is also ATP-dependent (Gibbs et al., 2015). Therefore, mitochondrial ATP synthesis is essential to keep the brain functioning normally.

Glucose serves as the main source of energy in neurons. Initially, glucose catabolism generates pyruvate, which is then transferred to mitochondria for TCA and OXPHOS (Mergenthaler et al., 2013). By combining electron transport with the phosphorylation of ADP on the inner mitochondrial membrane (IMM), OXPHOS produces ATP. NADH CoQ reductase (complex I), succinate dehydrogenase (complex II), ubiquinol-cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V) are all involved in the process (Sousa et al., 2018; Vercellino and Sazanov, 2022).

Free radicals

Free radicals, particularly ROS, are generated by mitochondria. ROS acts a significant role in the regulation of multiple neuronal cell life processes, including nucleic acid oxidation, immune response, and NF-κB pathway. The major source of free radicals, also known as "mitochondrial ROS," is the electron transport chain (ETC). There is a strong correlation between the rate of ROS production, mitochondrial membrane potential (MMP), and the activity of the ETC complexes (Islam, 2017; Kalpage et al., 2019).

Cell death

To maintain organ size and function, mitochondria are required for cell death processes such as apoptosis, necroptosis, pyroptosis, and ferroptosis (Bock and Tait, 2020). The most widely understood mitochondria-related mechanism among them is apoptosis. Mitochondrial apoptosis also referred to as intrinsic apoptosis, is dependent on mitochondrial outer membrane permeabilization (MOMP). The procedure enables the release of proteins from the mitochondrial intermembrane space into the cytoplasm, which causes cell death. The establishment of functional circuitry, upkeep of healthy cell bodies and axons, promotion of myelination, and effective synaptic contact with target muscle are all facilitated by mitochondrial apoptosis in the brain (Buss et al., 2006; Fricker et al., 2018).

Neuroinflammation

Under certain stress conditions, the outer and inner membrane of mitochondria are damaged, and mitochondrial

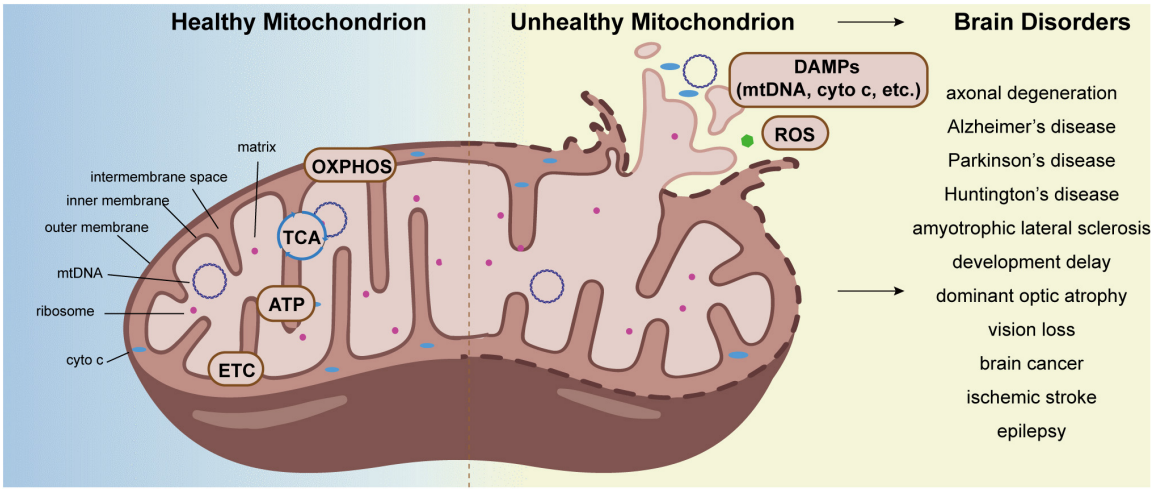

FIGURE 1
Aberrant mitochondrion causes brain disorders. The tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation (OXPHOS), electron transport chain (ETC), and ATP synthesis all take place primarily in mitochondria. Under stress, mitochondria produce DAMPs and excessive ROS, which cause a variety of brain disorders, including axonal degeneration, neurodegeneration diseases, dominant optic atrophy, epilepsy, and so on.

components such as mitochondrial DNA (mtDNA), formyl peptides, cytochrome c (cyto c) and cardiolipin are released into the cytoplasm, which is regarded as danger-associated molecular patterns (DAMPs), inducing the assembly and activation of the inflammasome, the release of cytokines and the elicitation of innate immune responses (Bader and Winklhofer, 2020). DAMPs released by mitochondria activate microglia in the brain, which represent the primary form of immune defense. In addition to oxidative stress, metabolism, and OXPHOS regulation, mitochondria play an important role in neuroinflammation (Regen et al., 2017; Gu et al., 2021; Zhao et al., 2021).

Mitochondrial quality control in the brain

Mitochondrial dysfunction causes various diseases in the brain. Mitochondria are semi-autonomous organelles, and their proteome includes about 1,500 human proteins, which are derived from the nuclear genome and mitochondrial genome (Morgenstern et al., 2017). Among them, only 13 proteins are encoded by the mitochondrial genome. About 99% of mitochondrial proteins are synthesized by cytosolic ribosomes, followed by sorted and imported to mitochondria. Mitochondria are the central sites for the development of the TCA and energy production, while also participates in cell metabolism, cell growth, cell death, inflammation, and cell homeostasis. Therefore, MQC mechanisms are essential to ensure proper protein folding and maintain a normal mitochondrial environment. The processes of MQC include mitochondrial morphology control (fission and fusion), macromitophagy (mitophagy), micromitophagy, and the mitochondrial protease system (**Figure 2**).

Mitochondrial morphology control

Mitochondria, as highly dynamic organelles, participate in calcium networks and apoptosis, which are coupled to molecular patterns signaling, amino acid and lipid metabolism, and cell death. Thus, the maintenance of mitochondrial integrity and homeostasis is critical, which is accomplished through continuous fusion and fission. The process by which two mitochondria fuse into one is known as mitochondrial fusion. Because of the double membranes, mitochondrial fusion includes both outer and inner membrane fusion. Three large dynamin-related GTP-hydrolyzing enzymes, mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 (OPA1) are involved in the fusion process (Bertholet et al., 2016; Chan, 2020). In particular, MFN1 and MFN2 are localized on the outer mitochondrial membrane (OMM) and are required for outer membrane fusion (Santel and Fuller, 2001; Rojo et al., 2002; Koshiba et al., 2004). Trans interactions between mitofusin are commonly accepted to mediate the tethering of mitochondria during the fusion process because they are present on opposing mitochondrial membranes and form homo-oligomeric and heterooligomeric complexes for fusion. Models of outer membrane fusion have been proposed. The crystal structures of the MFN1 suggest that an intermolecular interface of the globular GTPase domains modulates membrane tethering (Cao et al.,

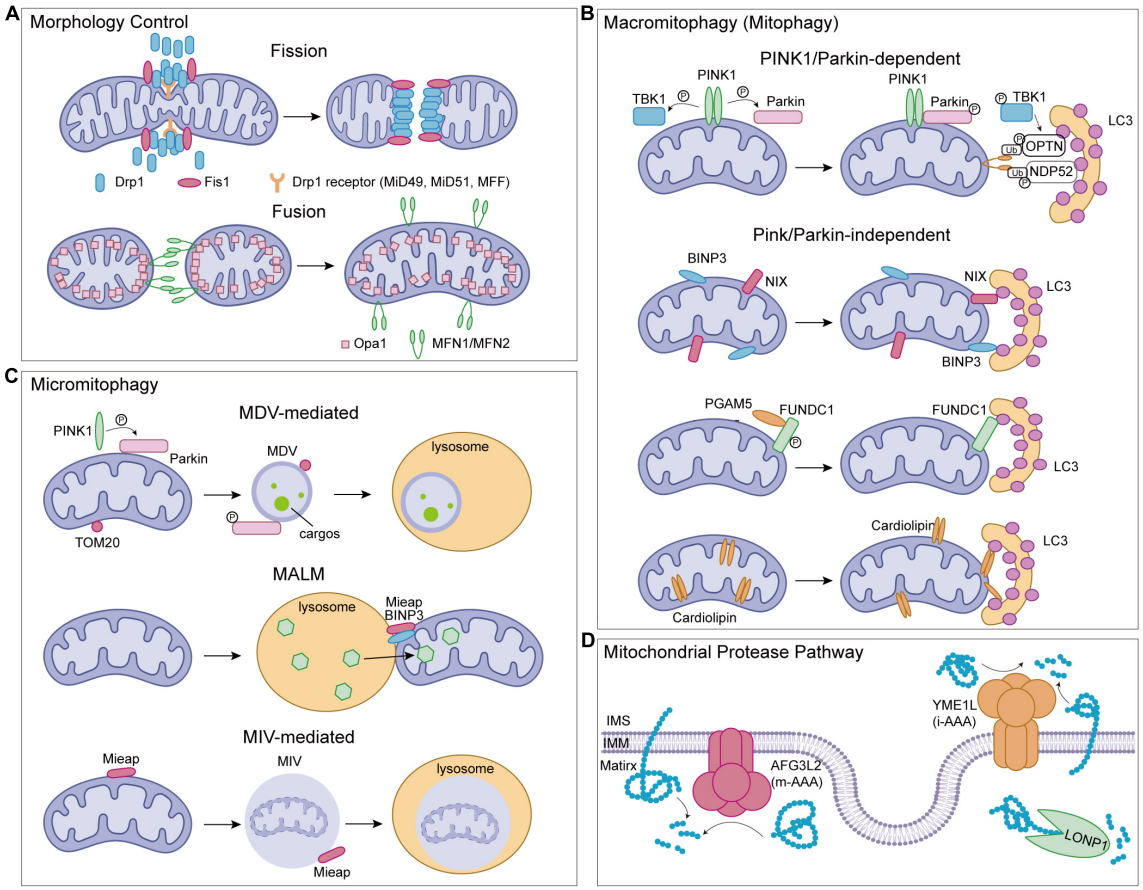

FIGURE 2
Mitochondrial quality control (MQC) pathways in human. **(A)** Mitochondrial morphology control. **(B)** Mitophagy pathways. **(C)** Micromitophagy pathways. **(D)** Mitochondrial protease pathways. Drp1, dynamic-related protein 1; Fis1, fission 1; MFF, mitochondrial fission factor; MiD49/MiD51, mitochondrial dynamics proteins 49/51; OPA1, optic atrophy 1; MFN1/MFN2, mitofusin1/mitofusin2; PINK1, serine/threonine-protein kinase PINK1; Parkin, E3 ubiquitin-protein ligase parkin; LC3, microtubule-associated protein light chain 3; TBK1, TANK binding kinase 1; NIX, NIP3-like protein X; BNIP3, Bcl-2/adenovirus E1B 19 kDa interacting protein 3; FUNDC1, FUN14 domain containing 1; PGAM5, phosphoglycerate mutase family member 5 phosphatase; Mieap, spermatogenesis-associated protein 18; TOM20, translocase of outer mitochondrial membrane 20; MDV, mitochondrial-derived vesicles; MALM, Mieap-induced accumulation of lysosome-like organelles within mitochondria; MIV, Mieap-induced vacuoles.

2017; Yan et al., 2018), whereas another model indicates that the C-terminal domain is also needed (Koshiba et al., 2004; Franco et al., 2016). It has recently been suggested that mitochondrial fusion tethers outer membranes through nucleotide-dependent dimerization (Qi et al., 2016; Cao et al., 2017). Following outer membrane fusion, OPA1 mediates mitochondrial inner membrane fusion. OPA1 is found in two topologically distinct isoforms in different tissues due to alternative splicing and proteolytic processing by mitochondrial proteases OMA1 and YME1L (Xiao et al., 2014; Wai et al., 2015; Anderson et al., 2020). Long-form OPA1 (L-OPA1) and cardiolipin are sufficient to facilitate membrane fusion, and loss of OMA1 delays neurodegeneration by preventing stress-induced OPA1 cleavage processing in mitochondria (Korwitz et al., 2016; Ban et al., 2017). In the OPA1-null cells, mitochondria could only show mitochondrial outer membrane fusion but never progress to inner membrane fusion. In this case, mitochondria appear to fission (Song et al., 2009; Mishra et al., 2014).

Fission is undeniably important for mitochondrial division and quality control, and dynamic-related protein 1 (Drp1) plays a key role in this process. Three Drp1 receptors, mitochondrial fission factor (MFF), mitochondrial dynamics proteins 49 (MiD49), and mitochondrial dynamics proteins 51 (MiD51), are all involved in recruiting Drp1 from the cytoplasm to the OMM. A fission defect similar to Drp1 depletion is generated by the loss of any of the receptors, which causes the mitochondria to elongate noticeably (Losón et al., 2013; Osellame et al., 2016; Otera et al., 2016). Fission 1 (Fis1), another OMM-located protein, has also been shown to recruit Drp1. Overexpression of Fis1 in cells promotes mitochondrial fragmentation, however, deletion of the *FIS1* gene has no

effect on mitochondrial morphology or Drp1 recruitment to mitochondria (Yoon et al., 2003; Stojanovski et al., 2004; Otera et al., 2010). Drp1 undergoes structural changes after being recruited to mitochondria, constricting the mitochondrial tubule and inducing mitochondrial fission. The cryo-EM studies indicate that cardiolipin, a lipid enriched in mitochondrial membranes, can modulate the Drp1 structure and thus activate the fission process (**Figure 2A**; Francy et al., 2017).

Macromitophagy (Mitophagy)

Autophagy is an important quality control system in the nervous system. In mammals, three different types of autophagy processes have been described: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). The primary mechanism of MQC in cells is the macroautophagic degradation of mitochondria, or mitophagy, which is necessary for basal mitochondrial turnover.

In the process of mitophagy, dysfunctional mitochondria are first detected, then separated from the mitochondrial network, and recruited by the mitophagosome. The mitophagosome structures are formed in the absence of the ATG8 family proteins, which are classified as microtubule-associated protein light chain 3 (LC3, including LC3A, LC3B, and LC3C) and GABARAP (GABARAP, GABARAP-L1, and GABARAP-L2) subfamilies. Fusion of mitophagosome with lysosomes for degradation is necessary for the last stage of the elimination of damaged mitochondria (Tsuboyama et al., 2016; Onishi et al., 2021). Four major mitophagy pathways include serine/threonine-protein kinase PINK1 (PINK1)/E3 ubiquitin-protein ligase parkin (Parkin)-mediated mitophagy, Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3)/NIP3-like protein X (NIX)-regulated mitophagy, FUN14 domain containing 1 (FUNDC1)-mediated mitophagy, and lipid-related pathways (**Figure 2B**). To trigger the degradation process, members of the ATG8 family should interact with all four pathways.

PINK1/Parkin-mediated mitophagy is the most well-known pathway. PINK1 is found on the IMM of normal mitochondria and is rapidly degraded by the mitochondrial membrane peptidase and presenilin-associated rhomboid-like protease (PARL) (Mokranjac and Neupert, 2007; Meissner et al., 2011). As a result, PINK1 remains at a low level under healthy conditions. However, when the inner membrane potential is depolarized, PINK1 moves to the OMM instead of IMM to form a dimer and is auto-phosphorylated at Ser228 and Ser402 residues (Okatsu et al., 2012). After being phosphorylated at Ser65 in its ubiquitin-like (Ubl) domain and activated by PINK1, Parkin, one of the E3 ubiquitin ligases, ubiquitinates its substrates like mitofusin (Kondapalli et al., 2012; Shiba-Fukushima et al., 2012; Koyano et al., 2014; Onishi et al., 2021). The autophagy adaptors, such as OPTN and NDP52, are phosphorylated by TANK-binding kinase 1 (TBK1), which recognizes these poly-ubiquitin chains, and binds with autophagy-related ATG8 family proteins via LIR motif, leading to mitophagy (Narendra et al., 2010; Kane et al., 2014; Kazlauskaite et al., 2014; Heo et al., 2015; Okatsu et al., 2015; Ordureau et al., 2015).

Unlike PINK1/Parkin, the BNIP3/NIX pathway is activated independently of changes in mitochondrial membrane potential (Rikka et al., 2011). In the normal state, BNIP3 is typically expressed as an inactive monomer in the cytoplasm, but under the hypoxia condition, BNIP3 is up-regulated, homodimerized, and anchored to the OMM by its C-terminal domain, while simultaneously exposing its N-terminal domain to the cytoplasm (Ray et al., 2000; Kubli et al., 2008; Hanna et al., 2012). At the N-terminal domain of BNIP3, the LC3-interacting region (LIR) motif recognizes and binds LC3, and mutations in the LIR motif prevent the contact with LC3, resulting in mitophagy abnormalities. Besides, phosphorylation at Ser17 and Ser24 near the LIR motif of BLIP3 is also important for BNIP3-LC3 interactions (Zhu et al., 2013). NIX is homology to BNIP3 and contains an LIR motif binding to ATG8 family members LC3A, LC3B, GABARAP, GABARAP-L1, and GABARAP-L2 among others (Hamacher-Brady et al., 2007; Sandoval et al., 2008; Novak et al., 2010). Ser34 and Ser35 of NIX, two serine residues close to the LIR motif, are phosphorylated similarly to BNIP3 in order to stabilize NIX-LC3 interactions and induce mitophagy (Rogov et al., 2017).

Additionally, the FUN14 domain containing 1 (FUNDC1) is also an OMM protein that has an LIR motif. It contains a characteristic LIR motif close to the N-terminus and three transmembrane domains (Liu et al., 2012). Phosphorylation and dephosphorylation on residues Ser13 and Tyr18 near the LIR motif of FUNDC1 regulate the process of mitophagy. Under hypoxia conditions, FUNDC1 interacts with LC3 via phosphoglycerate mutase family member 5 phosphatase (PGAM5) dephosphorylation at Ser13, and FUNDC1 phosphorylated by CK2 can reverse the effect of PGAM5 on mitophagy activation (Chen G. et al., 2014). In addition, SRC tyrosine kinase mediates the phosphorylation of Tyr18 to negatively regulate the FUNDC1-LC3 interactions field (Chen et al., 2016). Moreover, the phosphorylation of Ser17 in FUNDC1 by ULK1 enhanced the interaction between FUNDC1 and LC3, which could promote the mitophagy process (Wu et al., 2014).

Likewise, lipids including cardiolipin, cholesterol, and fatty acids have a role in the regulation of mitophagy. Among them, cardiolipin is a mitochondria-specific phospholipid located in IMM and is involved in receptor-mediated mitophagy in cells (Chu et al., 2013). When oxidized, cardiolipin is redistributed and translocated from IMM to OMM in damaged mitochondria and recognized by LC3. This process is coordinated by a hexameric intermembrane space protein, NDPK-D. The knockdown of endogenous NDPK-D decreases

cardiolipin externalization and mitochondrial degradation (Kagan et al., 2016). Meanwhile, fatty acids could support the stability of PINK1 and translocation of the Parkin protein, participating in the regulation of mitophagy in the presence of PINK1. In the meantime, it has been shown that cholesterol has a dual role in PINK1/Parkin-mediated mitophagy (Roca-Agujetas et al., 2021).

Micromitophagy

Micromitophagy, which is defined as mitochondrial degradation independent of mitophagosomes, is another MQC mechanism that ensures mitochondrial homeostasis (**Figure 2C**; Wang et al., 2022). Under oxidative stress, mitochondria can generate mitochondrial-derived vesicles (MDVs) to proceed micromitophagy. In mammalian cells, MDVs formation is required OMM protein TOM20, or PINK1, Parkin, and soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs). Recognition and initiation of micromitophagy are different from the mechanism mediated by canonical autophagy regulators such as ATG5 or LC3 (Soubannier et al., 2012; McLelland et al., 2014, 2016; König et al., 2021). Internalization of MDVs into the lysosomal lumen for degradation occurs following the formation of MDVs (Soubannier et al., 2012; Wang et al., 2022). An alternative micromitophagy mechanism known as spermatogenesis-associated protein 18 (SPATA18; also called Mieap)-induced accumulation of lysosome-like organelles within mitochondria (MALM) is characterized by the transfer of lysosomal proteins into mitochondria to destroy the oxidized mitochondrial protein. This process varies from MDVs uptaking microautophagic payloads into lysosomes (Kitamura et al., 2011; Nakamura et al., 2012). Under mitochondrial stress, Mieap is up-regulated and works with BNIP3 to promote MALM (Nakamura et al., 2012). When mitochondria are severely damaged or MALM is inhibited, Mieap-induced vacuoles (MIVs) uptake the entire damaged mitochondria into the lysosome for decay (Kitamura et al., 2011; Miyamoto et al., 2011). Although the micromitophagy processes have been characterized in yeast and some mammalian cells such as hepatocytes, its role in brain and brain-related diseases need to be further investigated (Kissová et al., 2007; Bhatia-Kiššová and Camougrand, 2010; Lemasters and Zhong, 2018).

Mitochondrial protease system

Mitochondrial proteome is encoded by both nuclear- and mitochondrial-genome. The fidelity and synchronization of these two protein synthesis systems are essential for ATP production and mitochondrial function. The nuclear-encoded proteins are synthesized by cytosolic ribosomes and imported into mitochondria by elaborate machinery embedded in the outer and inner mitochondrial membrane. During this coordination, the production of mitochondrial encoded proteins is regulated by the levels of imported proteins, preventing the redundant unassembled subunits (Ott et al., 2016; Priesnitz and Becker, 2018). The mitochondrial proteases could remove the unassembled proteins of the IMM. Furthermore, upon being imported into mitochondria, proteins synthesized by cytosolic ribosomes are monitored by mitochondrial proteases. Mitochondria have various mitoproteases, which can be divided into processing peptidases, ATP-dependent peptidases, and other mitochondrial peptidases (Deshwal et al., 2020). Among them, mitochondrial processing peptidases remove sorting signals from newly imported nuclear-encoded proteins, which is required for the maturation of many mitochondrial proteins (Mossmann et al., 2012; Poveda-Huertes et al., 2017; Deshwal et al., 2020). The mitochondrial processing protease MPP, for example, cleaves off mitochondrial targeting sequences (MTSs) in the matrix (Mach et al., 2013). Meanwhile, the inner membrane protease (IMMP) or ATP23 promotes the maturation of some proteins into the intermembrane space (IMS) (Weckbecker et al., 2012).

Another type of MQC-related protease is ATP-dependent proteases, which are the core consistency of the mitochondrial proteolytic system, activating in all mitochondrial compartments. The LONP1, caseinolytic mitochondrial matrix peptidase (CLPXP), m-AAA protease, and i-AAA protease are the four ATP-dependent proteases. LONP1 regulates mitochondrial oxidative phosphorylation (OXPHOS) via degrading damaged aconitase, and enzyme of the Krebs cycle in the mitochondrial matrix (**Figure 2D**; Bota and Davies, 2016). Besides, LONP1 modulates mitochondrial gene expression and some protein maturation (Lagouge et al., 2015; Zurita Rendón and Shoubridge, 2018). LONP1 also facilitates degrade COX4-1 to promote the assembly of the terminal electron transport chain (ETC) enzyme cytochrome c oxidase (Sepuri et al., 2017). Because of the critical role of LONP1 in mitochondrial functions, abnormal LONP1 causes a variety of diseases in humans. CLPXP, other than LONP1, is also reported to participate in the degradation of damaged OXPHOS complex I and II subunits (Seo et al., 2016). Meanwhile, CLPXP regulates gene expression by controlling the mitochondrial RNA (mtRNA) stability (Matsushima et al., 2017).

The m-AAA and i-AAA proteases are mitochondrial membrane-localized proteases (**Figure 2D**). They are necessary for the proteolysis of misfolded or damaged proteins and some IMM proteins, which helps to maintain the stability of mitochondria. In mammalian mitochondria, the m-AAA protease is composed of either an AFG3L2 homohexamer or an AFG3L2 and SPG7 heterohexamer. The hexameric AAA protease p97 (VCP) has a critical role in the degradation of outer mitochondrial membrane proteins, such as MFN1 (Xu et al., 2011), and the i-AAA protease YME1L removes translocase of the inner membrane 17A protein (TIM17A) to

reduce protein import into mitochondria under stress and also regulates mitochondrial lipid composition by degradation of some lipid transfer proteins that shuttle phospholipids across the intermembrane space between the OMM and the IMM (Rainbolt et al., 2013; Saita et al., 2018). Additionally, the IMM proteases also regulate mitochondrial morphology by cleaving OPA1. Deletion of YME1L in the nervous system causes spinal cord axon degeneration in mice. Ablation of metalloproteinase OMA1, which is located on IMM, prevents neurodegeneration in YME1L-mutant mice, demonstrating the role of proteolytic processing in regulating mitochondrial function and physiology in the brain (Sprenger et al., 2019). In addition, the OMM-located ATPase family AAA domain-containing 1 (ATAD1) may promote the extraction and degradation of mislocalized tail-anchored (TA) proteins to preserve mitochondrial integrity, performing a crucial role in the regulation of synaptic activities in neurons (Chen Y. C. et al., 2014; Han et al., 2020).

Aberrant mitochondrial quality control and brain disorders

Mitochondrial dysfunction impairs mitochondrial respiration, energy generation, mitochondrial oxidative stress, and cell death (Martin, 2010; Yin et al., 2016; Stefanatos and Sanz, 2018; Bader and Winklhofer, 2020). Prior studies have largely focused on how abnormal MQC contributes to various neurological diseases. As an essential part of the nervous system, brain abnormality has always been linked to mitochondrial dysfunction. Here, we briefly outline some MQC disruption-related brain disorders and set out to summarize identified proteins in pathological pathways.

Neurodegenerative diseases

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by the loss of selective neuron subtypes in the CNS. It has been demonstrated that the aberrant MQC plays a significant role in the progression of these diseases. If we take AD as an example, the mitochondrial fission and fusion proteins are disrupted in the hippocampus in various AD animal models and AD patients. The fission protein Fis1 is up-regulated, while fusion proteins MFN1, MFN2, and OPA1 are down-regulated (Wang et al., 2009). Moreover, Drp1 phosphorylation at Ser616 is higher in the brains of AD patients (Wang et al., 2009). Even though Parkin-mediated mitophagy was initially characterized in PD, the Parkin protein level has been shown higher and Parkin-mediated mitophagy is ineffective in the brains of AD patients (Ye et al., 2015). In addition, abnormal MQC and dysfunctional mitochondria are associated with chronic inflammation. It is well-known that, activated microglia function as innate immune cells in the CNS. In AD mice and patients, as observed, microglia stimulate phagocytosis, clearance, and degradation to minimize the accumulation of Aβ (Graeber et al., 2011). However, chronic microglia activation leads to the secretion of inflammatory cytokines and further neuronal dysfunction (Jiang et al., 2012). These findings suggest that aberrant MQC contributes to the development of neurodegenerative diseases.

Ischemic stroke

Ischemic stroke is one of the major diseases that cause death and disability of the nervous system. Although revascularization via reperfusion has led to a reduction in the mortality rate of ischemic stroke, the reperfusion itself also causes additional damage to the brain tissue, which is called ischemia-reperfusion (I/R) injury. It has been suggested that several MQC-related processes contribute to I/R damage. The removal of damaged mitochondria and mitochondrial apoptosis of neuron cells is aided by mitochondrial fission and mitophagy during cerebral I/R injury (Kumar et al., 2016; Zhao et al., 2018b). Overexpression of Sirtuin 3 (Sirt3) can inhibit mitochondrial fission and trigger pro-survival signals in neurons subjected to I/R injury (Zhao et al., 2018a). Furthermore, excessive mitochondrial fission stimulates energy imbalance and mtDNA damage, which worsens brain damage (Yue et al., 2015).

Epilepsy

Epilepsy is typified by recurrent unprovoked seizures of neurons. Mitochondrial stress and MQC are involved in the pathogenesis of epilepsy. The levels of MQC-related proteins OPA1, MFN2, MFF, and Drp1 are elevated in the mice models of acute maximal electroshock and 6 Hz 44 mA seizure (Cho et al., 2022). MQC-related serine peptidase LONP1 is up-regulated in the mitochondria during status epilepticus (SE), and LONP1 knockdown enhances SE-induced mitochondrial apoptosis in neuron (Kim et al., 2021).

Mitochondrial quality control-related gene mutation or abnormal expression

Mitochondrial quality control-related gene mutation or abnormal expression is related to brain dysplasia (**Table 1**). In cultured neurons, over-expression of MFN2 mutation disrupted axonal mitochondrial positioning and promoted axon degeneration (Detmer and Chan, 2007; Misko et al., 2012). Moreover, neuron-specific knockout mice show that MFN2 is required for dendritic outgrowth, axonal projection, and

TABLE 1 Mitochondrial quality control gene abnormality-related diseases.

Gene	Protein	Variation/Regulation	Symptom/Disease	References
Mitochondrial morphology				
DNM1L	Drp1	Heterozygous or *de novo* mutations	Multisystem failure, including microcephaly, optic atrophy, hypoplasia, lactic acidemia epilepsy, epileptic encephalopathy and development delay	Waterham et al., 2007; Vanstone et al., 2016; Verrigni et al., 2019
		Phosphorylation at Ser616	AD, PD	Wang et al., 2009; Han et al., 2020
OPA1	OPA1	Autosomal dominant	Vision loss, optic nerve dominant optic atrophy (DOA), and DOA plus, Behr syndrome (BEHRS)	Alexander et al., 2000; Amati-Bonneau et al., 2008; Carelli et al., 2015
		Down-regulated	AD	Wang et al., 2009
MFN2	MFN2	Recessive mutation	Canine fetal-onset neuroaxonal dystrophy	Fyfe et al., 2011
		Down-regulated	AD	Wang et al., 2009
MEF2B	MEF	Recessive mutation	Delayed childhood development, optic atrophy, seizures, peripheral neuropathy, hypotonia	Shamseldin et al., 2012; Koch et al., 2016
Mitophagy				
PARK6	PINK1	Mutation	PD	Valente et al., 2001, 2002, 2004
PARK2	Parkin	Mutation	PD	Kitada et al., 1998; Lücking et al., 1998
		Up-regulated	AD	Ye et al., 2015
HDAC6	HDAC6	Mutation	Chondrodysplasia with platyspondyly, distinctive brachydactyly, hydrocephaly, and microphthalmia (CDP-PBHM), PD	Lee et al., 2010; Simon et al., 2010
Mitochondrial proteases				
LONP1	LONP1	Mutation	Cerebral, ocular, dental, auricular, and skeletal (CODAS) syndrome	Strauss et al., 2015; Peter et al., 2018
AFG3L2	AFG3L2	Dominant mutation	Spinocerebellar ataxia, spastic ataxia (SCA28), optic atrophy 12 (OPA12)	Di Bella et al., 2010; Caporali et al., 2020
		Recessive mutation	Spastic ataxia 5 (SPAX5)	Pierson et al., 2011
YME1L	YME1L1	Mutation	Mitochondriopathy with optic atrophy	Hartmann et al., 2016

survival (Chen et al., 2003, 2007; Lee et al., 2012; Pham et al., 2012). It has been improved that OPA1 can protect neurons from excitotoxicity (Jahani-Asl et al., 2011; Nguyen et al., 2011; Kushnareva et al., 2013). Some research shows heterozygous *OPA1* mutations both on the GTPase or GED domains lead to a decrease of protein quantity and mice of *Opa1* heterozygous mutations have become autosomal dominant optic atrophy (DOA) models. These DOA mice perform retinal ganglionic cell (RGC) loss or dysfunction and optic nerve dysfunction including axonal degeneration and demyelination (Williams et al., 2011). Moreover, mutations of mitophagy-associated gene *PARK6* (encoded PINK1) or *PARK2* (encoded Parkin) contribute to autosomal recessive juvenile parkinsonism (Lücking et al., 1998; Valente et al., 2001, 2002, 2004).

Potential of mitochondrial quality control-related targets for brain disorders

Mitochondrial quality control-related protein inhibitors and agonists have been recently shown to suppress pathological processes by regulating mitochondrial functions, including nervous system diseases, cardiovascular diseases, metabolic diseases, and cancer. In light of this, researchers are looking into whether MQC-related proteins can be drug targets for these diseases. For instance, a small molecule SIRT1 activator, SRT-1720, markedly improves renal tubular pathology and overall renal function in adult mice following I/R via regulating mitophagy (Fan et al., 2013). Mdivi-1, the inhibitor of Drp1, can induce apoptosis of hepatocellular carcinoma cells, suggesting a new approach of targeting MQC in cancer treatment (Akita et al., 2014; Wang et al., 2015; Lin et al., 2020). Thus, MQC-related proteins may become possible targets for disease treatment. Likewise, MQC is crucial for preserving healthy mitochondria and preventing the pathological effects of dysfunctional mitochondria in the brain. MQC-related targets, accordingly, represent potential future therapeutic strategies for brain diseases.

The mitochondrial morphology-associated protein Drp1 is highly expressed in the brain, implying that it is an important component in the brain. It has been demonstrated to modulate both the death of the neuronal cell and the

TABLE 2 Mitochondrial quality control (MQC)-associated proteins and therapeutic agents in brain diseases.[a]

Target	PDB code[b]	Treatment	Indications/Condition	Highest phase	References
Mitochondrial morphology					
Drp1	4BEJ, O00429	Mdivi-1	AD, HD, PD	Biological testing	Cui et al., 2010; Manczak and Reddy, 2012; Fröhlich et al., 2013; Rappold et al., 2014; Bido et al., 2017; Reddy et al., 2017; Wang et al., 2017
		P110/P110-TAT	ALS, HD	Preclinical	Joshi et al., 2018
		Lenti-Drp1-S579A	Neurodegenerative diseases	Biological testing	–
Fis1	1NZN, 1PC2, Q9Y3D6	P110	ALS, PD, HD	Preclinical	Suzuki et al., 2003; Dohm et al., 2004; Joshi et al., 2018
OPA1	6JTG, O60313	STK-002	Dominant optic atrophy	Preclinical	Yu et al., 2020
		VP-002	Ocular genetic disorders	Preclinical	–
		NFS-05 rAAV2-OPA1	Optic neuropathy	Preclinical	–
		rAAV2-hOPA1	Optic neuropathy	Biological testing	–
		pAAV2-OPA1-ND4	Leber hereditary optic neuropathy	Biological testing	–
MFN1	5GNU, 5YEW, 5GOE, Q8IWA4[c]	MiM-111	ALS, HD, PD	Biological testing	Qi et al., 2016; Cao et al., 2017; Yan et al., 2018
		Chimera-C Regeneurin-C	AD, PD, HD	Biological testing	–
MFN2	6JFK, 6JFM, O95140[c]	MiM-111	ALS, HD, PD	Biological testing	Li et al., 2019
		Chimera B-A/l/, Mfn2-367-384Gly-TAT/TAT-367-384Gly	Charcot-Marie-Tooth disease, type 2A	Preclinical	–
		MASM-7	Neurological disorders	Biological testing	–
		Chimera-C Regeneurin-C Mitolityn-4 Regeneurin-C/O	AD, PD, HD	Biological testing	–
MiD49	5WP9, Q96C03[c]	–	–	–	Kalia et al., 2018
MiD51	4NXT, Q9NQG6[c]	–	–	–	Richter et al., 2014
MFF	Q9GZY8[c]	–	–	–	–
Mitophagy					
PINK1	Q9BXM7[c]	MTK-115	HD	Biological testing	–
		BC1464	PD	Biological testing	Liu et al., 2020
		MTK-0034/0030/0043	PD	Biological testing	–
Parkin	5N38, O60260[c]	–	–	–	Kumar et al., 2017
FUNDC1	2N9X, 5GMV, Q8IVP5[c]	–	–	–	Kuang et al., 2016; Lv et al., 2017
ULK1	6QAS, O75385[c]	VMY-BC-1	Brain cancer	Preclinical	Chaikuad et al., 2019
		BL-918	PD	Preclinical	–
TBK1	6NT9, Q9UHD2[c]	GSK-8612	Neurological disorders	Biological testing	Zhang et al., 2019
BNIP3	2J5D (Bocharov et al., 2007), Q12983[c]	–	–	–	Bocharov et al., 2007
NIX	O60238[c]	–	–	–	–
PGAM5	5MUF, Q96HS1[c]	–	–	–	Chaikuad et al., 2017
Beclin 1	7BL1, Q14457[c]	–	–	–	Tremel et al., 2021
Beclin 2	5K7B, 5K9L, A8MW95[c]	–	–	–	Koentjoro et al., 2017
SIRT1	5BTR, Q96EB6[c]	SRTAW-04	Neurodegeneration	Preclinical	Cao et al., 2015

(Continued)

TABLE 2 (Continued)

Target	PDB code[b]	Treatment	Indications/Condition	Highest phase	References
Mitochondrial proteases					
p97 (VCP)	7RLF	KUS-121	Central retinal artery occlusion (CRAO), PD, Glaucoma Retinal degeneration Stroke, ischemic	Phase I/II	Hasegawa et al., 2016, 2020; Hanako Ohashi et al., 2020; Caffrey et al., 2021
		KUS-187	Ocular genetic disorders	Priclinical	–
LONP1	7OXO	BT-317	Glioblastoma multiforme therapy	Biological testing	Mohammed et al., 2022
AFG3L2	2LNA, 6NYY, Q9Y4W6[c]	–	–	–	Ramelot et al., 2013; Puchades et al., 2019
YME1L1	Q96TA2[c]	–	–	–	–

[a]Part of the data from *Cortellis Drug Discovery Intelligence* database.
[b]For some target proteins, there are a considerable number of PDB codes, and only some of the results are shown here.
[c]AlphaFoldDB of the target proteins.

survival of post-mitotic neurons (Cribbs and Strack, 2007; Kageyama et al., 2012). The inhibitor of Drp1, Mdvi-1, provides neuroprotection *in vitro* and *in vivo* (Cassidy-Stone et al., 2008; Park et al., 2011; Grohm et al., 2012). Pre- and post-treated AD or PD cells with Drp1 inhibitor Mdivi-1 show decreasing interaction between Drp1 and phosphorylated tau, reducing Aβ or α-syn aggregates, suppressing mitochondrial dysfunction, and maintaining cell viability, mitochondrial dynamics, mitochondrial biogenesis, and synaptic activity, indicating neuroprotection effects (Manczak and Reddy, 2012; Reddy et al., 2017; Wang et al., 2017). Meanwhile, inhibition of mitochondrial fission also suppresses the progress of ALS. The SOD1G93A mouse model is used for preclinical testing of treatments for ALS (Gurney et al., 1994). P100, which inhibits the interaction of Drp1 and Fis1, improves the mitochondrial structure and function by reducing oxidative stress in this model. Besides, P110 treatment also suppresses mitochondrial dysfunction in motor neurons and patient-derived fibroblasts, suggesting that Drp1 may be a drug target in ALS therapy strategy (Joshi et al., 2018). Furthermore, treatment with mitochondrial-targeted donor AP39 can transfer mitochondrial fission to fusion by increasing OPA1 and MFN1 levels and decreasing Fis1 levels in early-onset AD model APP/PS1 neurons and transgenic mice (Cassidy-Stone et al., 2008; Park et al., 2011; Grohm et al., 2012).

Mitophagy-associated proteins and mitochondrial proteases are also potential drug targets for brain diseases. Compound BC1464, which disrupts the FBXO7/PINK1 interaction, can rescue mitophagy and provides neuroprotection in PD models (Liu et al., 2020). The ATPase inhibitor, KUS121, improves the average readable letter counts, visual field scores, and retinal sensitivities of all nine patients with acute central retinal artery occlusion (CRAO) in phase I/II clinical trial (Hanako Ohashi et al., 2020). In the meanwhile, KUS121 shows the effect of preventing retinal ganglion cell death in animal models of glaucoma (Nakano et al., 2016).

As can be seen, these studies indicate that MQC-associated proteins are suitable as therapeutic pharmaceutical targets for brain disorders (**Table 2**).

Conclusion and perspective

In this review, we discuss the physiological roles of mitochondria and the MQC mechanism in the brain. MQC not only plays a vital role in maintaining mitochondrial morphology and functioning, but also participates in the pathological progression of a range of brain illnesses. Regulation of MQC through the pharmacological intervention of mitochondrial morphology, mitophagy, or the activity of mitochondrial proteases is emerging as a strategy for the treatment of mitochondrial-associated brain disorders.

Although MQC regulation can improve the process of brain disease, only a few regulators of MQC-related proteins have been identified as novel therapeutic targets or used in preclinical research (**Table 2**). Thus, there is still a lack of effective regulators, and developing targeted drugs is incredibly challenging. Because of the massive data sets available for drug candidates, computer-aided drug design (CADD) offers new approaches to efficacy and safety evaluations of drug candidates based on big data modeling, artificial intelligence modeling, and molecular docking (Zhu, 2020). This targeted drug development is dependent on the protein structure of the target (Yang et al., 2021). Some MQC-related essential proteins' structures have been analyzed or predicted as structural biology and structure prediction methods have advanced, but PDB structures of full-length proteins under different conditions, as well as functional complexes, require further investigation (**Table 2**).

Finally, as we reviewed, although it is of bright prospects to develop MQC-related proteins as novel drug targets for brain disorders, the treatment of which still has a long way

to go. Meanwhile, when some MQC-regulated drugs are in clinical trials, larger-scale clinical studies will be required to verify the safety and effectiveness of the drugs. Hence, in the future, more in-depth understanding of MQC would give rise to the development in the treatment of neurological related diseases, upon which more innovative therapeutic options will come to fruit.

Author contributions

HY and XS conceived the topic for this review. XS, PS, and HZ prepared the figures and tables. All authors listed wrote the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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