Mitochondrial dysfunction in chronic neuroinflammatory diseases (Review)

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Abstract. Chronic neuroinflammation serves a key role in the onset and progression of neurodegenerative disorders. Mitochondria serve as central regulators of neuroinflammation. In addition to providing energy to cells, mitochondria also participate in the immunoinflammatory response of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis and epilepsy, by regulating processes such as cell death and inflammasome activation. Under inflammatory conditions, mitochondrial oxidative stress, epigenetics, mitochondrial dynamics and calcium homeostasis imbalance may serve as underlying regulatory mechanisms for these diseases. Therefore, investigating mechanisms related to mitochondrial dysfunction may result in therapeutic strategies against chronic neuroinflammation and neurodegeneration. The present review summarizes the mechanisms of mitochondria in chronic neuroinflammatory diseases and the current treatment approaches that target mitochondrial dysfunction in these diseases.

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1. Introduction

Neuroinflammation is a response orchestrated by the central nervous system (CNS) in response to infection and injury. The acute neuroinflammatory response reduces damage by promoting the repair of injured tissue. However, persistent stimulation leads to the transformation of the inflammatory response from acute to chronic, resulting in neuronal functional impairment and thus facilitates the progression of CNS diseases (1). Chronic neuroinflammation has been reported as a pathological feature present in several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and epilepsy, amongst other neurological disorders (2,3). The close association between neuroinflammation and neurodegeneration suggests that neuroinflammatory mechanisms may trigger neuronal degeneration, leading to neurotoxicity and a loss of neuronal cells.

Microglia, which are activated by pathological stimuli such as infections, foreign pathogens and neurodegeneration, produce chemotactic factors and proinflammatory cytokines, including nitric oxide, reactive oxygen species (ROS), interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α), to eliminate detrimental elements. Nonetheless, persistent stimulation can lead to an overabundance of inflammatory factors, which in turn inflict damage upon neurons (4). Likewise, astrocytes exhibit dual roles in neuroinflammation. In response to cerebral trauma, astrocytes undergo proliferation and transition into a neuroprotective state, fostering reparative and regenerative mechanisms such as remyelination (5). Conversely, in neuroinflammatory diseases, astrocytes are excessively activated into a neurotoxic state by cytokines secreted by microglia, releasing uncontrolled pro-inflammatory cytokines and complement proteins, which exacerbate damage to neighboring cells (6,7). Moreover, astrocytes facilitate lymphocyte movement across the blood-brain barrier, engage in antigen presentation between lymphocytes and microglia, and activate peripheral B cells and T cells via the lymphatic system, thereby amplifying the cerebral inflammatory cascade (1,8,9).

In the CNS, mitochondria serve as the primary energy source for cellular metabolic processes and are pivotal in regulating cellular metabolism, calcium signaling and programmed cell death (10). Neurons rely on mitochondrial oxidative phosphorylation (OXPHOS) to meet their energy demands, maintain ion gradients and facilitate neurotransmitter uptake

and recycling (11). Astrocytes contribute to the mitigation of neuronal and oligodendrocyte free fatty acid peroxidation and ROS generation through mitochondrial fatty acid β-oxidation (FAO), which accounts for ~20% of the brain's energy supply (12). Additionally, mitochondrial calcium ions modulate key enzymes of the tricarboxylic acid cycle, such as pyruvate dehydrogenase, thereby regulating OXPHOS (13). Mitochondrial calcium ions also regulate synaptic communication and excitability by modulating astrocytic proliferation and the release of excitotoxic glutamate (14). In addition, microglial mitochondria enhance migration and phagocytosis through calcium ion influx (15). Once mitochondrial dysfunction occurs, the mitochondria become insufficient to meet the heightened energy demands of overstimulated neurons and hyperactive glial cells, leading to abnormal cell metabolism and widespread cell death (10).

Mitochondrial dysfunction serves as both a cause and a consequence of chronic neuroinflammatory diseases. Neuronal mitochondrial dysfunction has been observed in AD, PD and amyotrophic lateral sclerosis (16-18). Chronic inflammation leads to the secretion of cytokines that sustain inflammation and redox stress, inducing mitochondrial DNA (mtDNA) damage (19). Correspondingly, damaged mitochondria can further induce persistent inflammatory responses and downstream pathological inflammation (20,21). A study has shown that inhibiting mitochondrial complex I activates microglia, whereas inhibiting mitochondrial fission reduces pro-inflammatory cytokine generation (12). Due to mitochondrial damage, overactivated microglia undergo a metabolic shift from OXPHOS to glycolysis, resulting in increased generation of ROS and reactive nitrogen species (RNS), thereby exacerbating the inflammatory response (22). Concurrently, microglia can induce the generation of pro-inflammatory astrocytes by releasing fragmented mitochondria (23). Furthermore, impairment of mitochondrial FAO in astrocytes contributes to the development of neuroinflammation and subsequent neurodegenerative processes (24). Additionally, the accumulation of damaged mitochondria in neurons can accelerate the progression of diseases by initiating programmed cell death (23). Mitochondria may therefore be a key link between chronic neuroinflammation and the pathogenesis of neurodegenerative diseases. Thus, repairing mitochondrial dysfunction may improve the outcomes of neurodegenerative diseases, such as AD and PD (25,26).

The aim of the present review was to summarize the molecular characteristics of mitochondrial dysfunction and provide potential directions for targeting mitochondria in the treatment of chronic neuroinflammatory diseases.

2. Pathogenesis of mitochondrial dysfunction

Mitochondrial dysfunction. Mechanisms of mitochondrial dysfunction involved in the progression and prognosis of chronic neuroinflammatory diseases include oxidative stress, epigenetics, mitochondrial dynamics and calcium homeostasis (27-32) (Fig. 1).

Oxidative stress. In normal, healthy cells, 90% of ROS are generated as a result of cellular respiration. During this process, electrons detach from the electron transport chain and attach to oxygen, producing superoxide anions (O_2^-) (33). Additionally, metal enzymes present within organisms utilize the interaction between oxygen and metal ions to generate ROS, which is a result of cellular metabolism (34). Conversely, normal cells also possess a protective system against free radicals, primarily composed of antioxidant enzymes such as glutathione peroxidase (GPX), non-enzymatic antioxidant factors, superoxide dismutase (SOD) and catalase (33). The excessive reduction of free radicals is catalyzed by antioxidant enzymes. SOD acts on O_2^- to produce hydrogen peroxide (H_2O_2), which has a lower oxidative capacity than O_2^-, while catalase and GPX enzymes, with the assistance of certain cofactors, convert H_2O_2 into H_2O. When this regulatory process is disrupted, ROS can inflict destructive damage on cells (33). Excessive ROS further induces peroxidation modifications of cellular macromolecules such as lipids, proteins, RNA and DNA (35). For instance, protein peroxidation may acquire toxic functions by forming cytotoxic aggregates. Therefore, the accumulation of ROS caused by various factors (such as increased oxygen consumption in the brain due to high energy demand, elevated levels of unsaturated fatty acids in neuronal membranes, high levels of redox transition metal ions, low antioxidant levels and neurotransmitter oxidation) makes the brain highly susceptible to the damaging effects of oxidative stress (36). The excessive generation of ROS, leading to oxidative stress, has emerged as a shared underlying mechanism implicated in multiple chronic neuroinflammatory disorders, such as AD and PD (37,38).

Due to being the primary source of ROS, mitochondrial dysfunction appears to be a potential focal point for the underlying pathology of neuroinflammation (39). Excessive free radicals damage the inner mitochondrial membrane, leading to compromised mitochondrial energy production and metabolism in the brain. This results in neuronal dysfunction and further exacerbates oxidative stress, promoting neuronal dysfunction and apoptosis. Furthermore, free radicals can directly or indirectly induce abnormal mitochondrial permeability transition pore (mPTP) function, indirectly altering the fluidity, permeability and osmotic properties of the mitochondrial membrane, thereby facilitating mPTP-related ROS release (40). Moreover, free radicals also interfere with electron transport chain (ETC) complexes, further promoting ROS generation (41). A study has also reported that mitochondrial ROS (mtROS) can lead to impairment of complex I within the mitochondrial ETC. This in turn results in a reduction of mitochondrial OXPHOS efficiency (42). This cycle formed by mitochondrial dysfunction and inflammation-related oxidative stress exacerbates the pathological damage in neuroinflammatory disorders.

Mitochondrial epigenetics. Epigenetic modifications within the mitochondria can influence mitochondrial gene expression and function. In neuroinflammatory conditions, heightened ROS production induces deleterious effects on mitochondrial respiration and OXPHOS, leading to DNA oxidation, rearrangements and mutations (43). mtDNA, with its elevated mutation rate and proximity to OXPHOS sites, is more susceptible to oxidative stress compared with nuclear DNA (43). Methylation is a primary epigenetic mechanism within mitochondria due to the absence of histones in mtDNA (44). Decreased mtDNA methylation levels have been observed in blood samples and postmortem brain tissues from individuals with

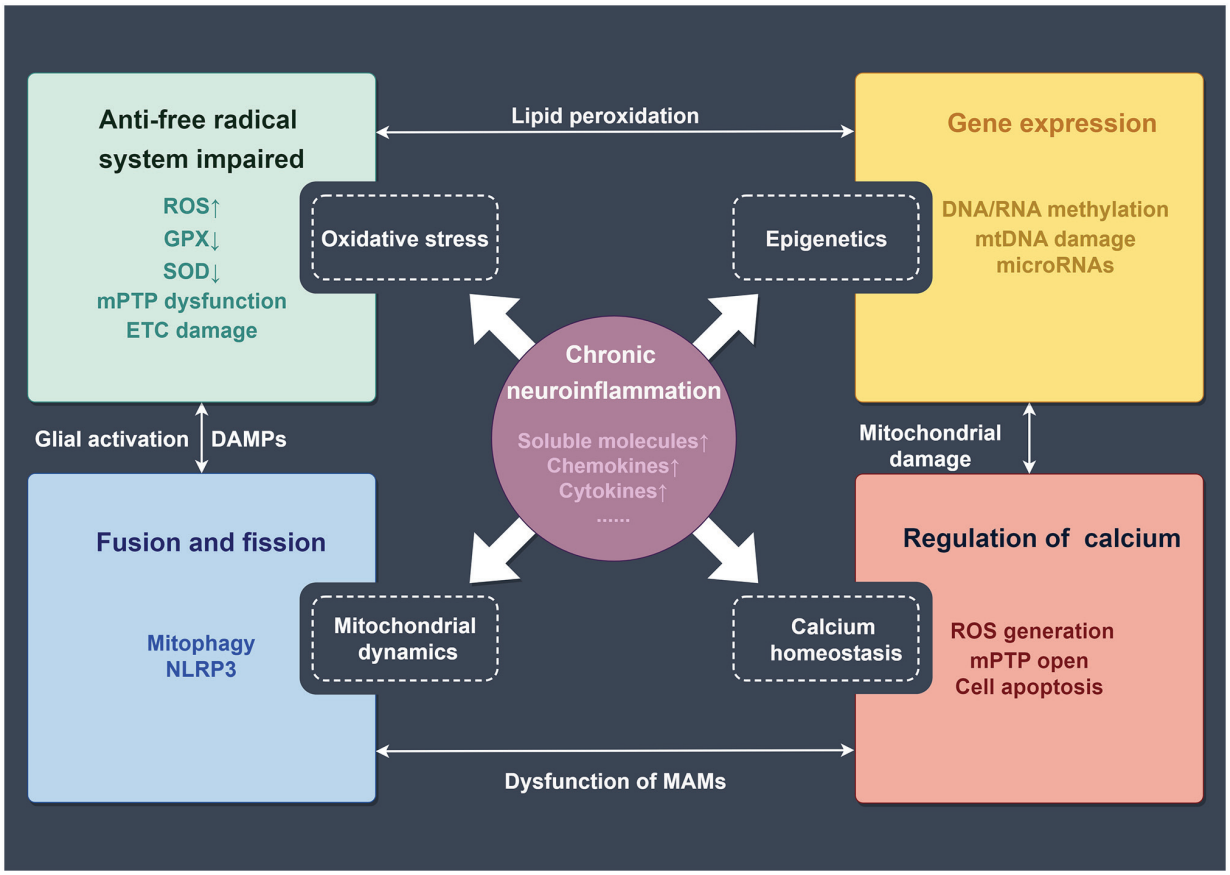

Figure 1. Crosstalk between mitochondrial dysfunction and neuroinflammation. ROS, reactive oxygen species; GPX, glutathione peroxidase; SOD, superoxide dismutase; mPTP, mitochondrial permeability transition pore; ETC, electron transport chain; DAMPs, damage-associated molecular patterns; mtDNA, mitochondrial DNA; MAMs, mitochondria-associated membranes; NLRP3, NLR family pyrin domain containing 3.

neuroinflammatory diseases (44). Additionally, chronic stress activates the hypothalamic-pituitary-adrenal axis, resulting in excessive glucocorticoid release and the regulation of mtDNA transcription and mtRNA expression (45). Conversely, mtDNA mutations exacerbate ROS production and trigger apoptosis through disruptions in the electron transport chain, impaired protein synthesis, and increased replication errors, influencing disease onset and progression (46). MtDNA damage results in impaired ETC function, reduced ATP generation, increased levels of ROS and disrupted calcium homeostasis, leading to exacerbated amyloid-β (Aβ) processing and aggregation in AD mice (47). Another study reported that Aβ induced mtDNA methylation, which persisted after the removal of Aβ and induced cognitive impairment in AD (48). Furthermore, non-coding RNAs are implicated in chronic low-grade systemic inflammation, known as inflammageing, impacting the energetic, oxidative and inflammatory status of senescent cells by modulating NF-κB/NLR family pyrin domain containing 3 (NLRP3) pathways and triggering senescence-associated secretory phenotype (43). Downregulation of microRNAs could also promote neuroinflammation by affecting the expression of genes critical for neuronal function and immune response in PD (49). It is evident that mitochondrial epigenetics is closely associated with the development of neuroinflammation. Understanding the regulatory role of mitochondrial epigenetics is therefore crucial for unraveling the underlying mechanisms of various neurological disorders.

Mitochondrial dynamics. The complex processes of mitochondrial fusion and fission collectively maintain mitochondrial functionality in the face of cellular metabolic or environmental stress (50). Mitochondrial fusion involves the merging of individual mitochondria, resulting in larger and interconnected networks. This process allows for the exchange of contents, including proteins, lipids and mtDNA, thereby promoting functional complementation and maintaining mitochondrial integrity. Mitochondrial fission is the opposite of fusion and involves the division of mitochondria into smaller fragments. Fission has a crucial role in quality control mechanisms, as it allows for the removal of damaged or dysfunctional portions of mitochondria through a process termed 'mitophagy' (51). Moreover, mitochondrial fission also facilitates the distribution of mitochondria throughout the cell (52).

Chronic neuroinflammation disrupts mitochondrial dynamics. Under neuroinflammatory conditions, dysfunctional mitochondria release ROS and damage-associated molecular patterns (DAMPs) (53), activating microglia and astrocytes, and triggering the release of pro-inflammatory cytokines and chemokines (54), thereby exacerbating the damage. In addition, disruption of mitochondrial dynamics can result in the accumulation of dysfunctional mitochondria, leading to increased susceptibility to inflammation-induced neuronal death. For instance, microglia can activate astrocytes into a neurotoxic state by releasing mitochondrial fragments and damaged mitochondria, further mediating extracellular

neuronal death in neuroinflammation (23). Furthermore, mitophagy also proves advantageous in eliminating impaired mitochondria and decreasing the infiltration of inflammatory molecules at the location where damaged mitochondria accumulate (55).

Mitochondrial dynamics may also have a significant involvement in inflammasome activation in chronic inflammation. Inhibition of dynamin-related protein 1 (Drp1) and overexpression of fusion proteins can attenuate inflammation-associated inflammasome responses (56). During RNA virus infection, mitofusin-2 interacts with NLRP3 to activate inflammasomes (57). Thus, molecules involved in mitochondrial dynamics may be crucial regulators of inflammasome activation. In summary, mitochondrial dynamics are essential for maintaining neuronal health and survival and a balanced fusion and fission process is beneficial for maintaining healthy mitochondrial function.

Mitochondrial calcium homeostasis. Mitochondrial calcium homeostasis holds significant importance in maintaining the functionality of neurons and glial cells (58). Mitochondrial function not only sustains the energy prerequisites of both spontaneous and induced neuronal activities in the brain through energy metabolism, but also governs neuronal signaling via uptake and cycling of mitochondrial calcium ions (59). Furthermore, the dynamic regulation of mitochondrial calcium homeostasis is also important for cell survival (13).

In the progression of neuroinflammatory diseases, calcium homeostasis remains a crucial molecular mechanism (60). The dysregulation of neuronal calcium homeostasis leads to oxidative stress, mitochondrial dysfunction, protein conversion disorders and neuroinflammation (61). Activated glial cells serve a crucial role in neuroinflammation and release soluble signaling molecules, including chemokines, pro-inflammatory cytokines, glutamate, prostaglandins, ROS, RNS and damaged mitochondria (62-64). Astroglial calcium signaling appears to be dysregulated in AD, which is potentially linked to the accumulation of Aβ in the brain (65). Depletion of mitochondrial calcium transporters has been shown to mitigate the inflammatory damage caused by glial cells activated by lipopolysaccharides (66).

Mitochondrial Ca^{2+} accumulation stimulates oxidative metabolism by modulating Ca^{2+}-sensitive dehydrogenases and metabolite carriers (67). Calcium homeostasis disruption can lead to an excessive buildup of matrix Ca^{2+} and subsequent initiation of the mPTP, thereby affecting mitochondrial function (68). This results in a decrease in ATP synthesis and an increase in ROS generation (69,70). Similar to Ca^{2+}, ROS also serve a crucial role in initiating the opening of the mPTP. This event results in mitochondrial swelling and impairment of the respiratory chain, thereby exacerbating oxidative stress-induced damage (71). Notably, mitochondria-associated membranes (MAMs) are specialized regions that regulate endoplasmic reticulum (ER) contact and transmit Ca^{2+} into mitochondria. These contact sites facilitate the exchange of various molecules, including lipids and signaling molecules, between the ER and mitochondria (72). Dysregulation of MAMs can therefore affect calcium signaling and disrupt communication between the ER and mitochondria, contributing to the activation of glial cells and the release of pro-inflammatory molecules (73,74). MAMs have also been found to regulate autophagy and mitochondrial dynamics (75). Dysregulation of MAMs has been observed in numerous neuroinflammatory disorders, such as AD and PD (76). These finding imply that targeting MAMs may hold promise as a therapeutic approach for the treatment of neuroinflammatory diseases.

3. Crosstalk of mitochondria in chronic neuroinflammation

AD. AD is a gradually advancing neurodegenerative condition characterized by the presence of Aβ and τ protein tangles, which are considered distinctive pathological markers. Aβ accumulation has also been observed within the mitochondria in the brains of patients with AD and transgenic AD mouse models (77,78). Aβ can directly disrupt the ETC and interfere with various mitochondrial matrix proteins and putative components of the mPTP, ultimately resulting in mitochondrial dysfunction (77-80).

In the early stages of AD, another often observed mitochondrial abnormality is the excessive generation of ROS, culminating in an upsurge of oxidative stress (81). Oxidative stress causes neuronal cell death, which contributes to the progressive cognitive decline seen in AD (82). Normally, mitochondria serve as pivotal guardians of the cellular redox equilibrium, orchestrating this balance via their antioxidant defense systems. However, malfunctioning mitochondria compromise these protective mechanisms, resulting in diminished scavenging of ROS and an escalation in oxidative harm (83). Furthermore, surplus ROS within mitochondria harms lipids and proteins. For instance, lipid peroxidation engenders the production of harmful byproducts such as malondialdehyde and 4-hydroxynonenal, intensifying the oxidative stress milieu (84). Concomitantly, protein oxidation can induce structural and functional impairments in mitochondrial proteins, thereby impacting energy synthesis and overall integrity. It is also worth noting that the heightened oxidative stress observed in AD can precipitate mutations, deletions and impairments in mtDNA repair mechanisms (85). These events further compound mitochondrial dysfunction, instigating a cycle of oxidative stress and neuronal damage.

Furthermore, DAMPs released from compromised mitochondria, coupled with elevated ROS levels, serve to intensify immune responses, with microglia playing a pivotal regulatory role in this process (86). On the one hand, activated microglia contribute to reducing neuroinflammation by phagocytosing and eliminating Aβ, while on the other hand, these microglia release pro-inflammatory cytokines and other inflammatory molecules, thus promoting inflammation (86,87). Notably, emerging research suggests that there is a bidirectional communication between mitochondria and microglia (88,89). Damaged mitochondria release mtDNA fragments into the cytoplasm, which can activate immune responses through Toll-like receptor 9, NLRP3 and stimulator of interferon genes (STING) signaling pathways. Microglia recognize these mtDNA fragments as danger signals and respond by releasing inflammatory mediators that further amplify the inflammatory microenvironment, inducing mitochondrial damage and subsequent cell death (89). This communication may also perpetuate neuroinflammation and contribute to the progression of AD. In addition, activation of the NLRP3 inflammasome is also an

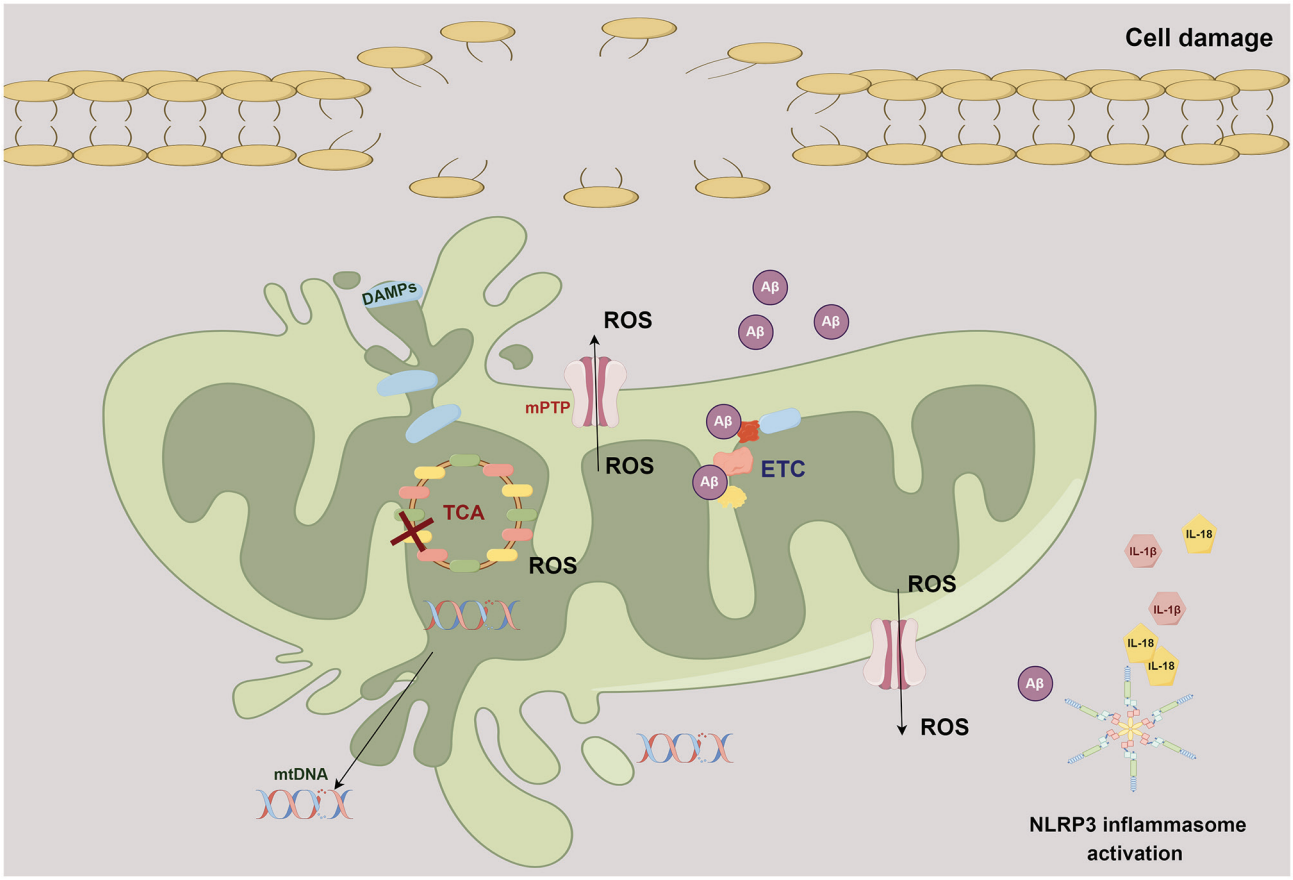

Figure 2. Mitochondrial dysfunction in Alzheimer's disease. ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; ETC, electron transport chain; DAMPs, damage-associated molecular patterns; mtDNA, mitochondrial DNA; NLRP3, NLR family pyrin domain containing 3; Aβ, amyloid-β; IL, interleukin; TCA, tricarboxylic acid (cycle).

important factor in the pathogenesis of AD (90,91), leading to the release of potent pro-inflammatory cytokines such as its effector molecule, IL-1β (92). Elevated IL-1β levels have been detected in the serum, cerebrospinal fluid and brain tissues of patients with AD (93). IL-1β can enhance the neuronal production of Aβ and induce τ protein phosphorylation, the blocking of which can alleviate neuroinflammation by reducing Aβ levels and τ activation (94,95). IL-18, another proinflammatory cytokine released when the NLRP3 inflammasome is activated, has been demonstrated to be correlated with susceptibility to sporadic late-onset AD (92,96). In conclusion, the neuroinflammatory process plays a crucial role in AD development, and understanding the intricate relationship between mitochondria and neuroinflammation in AD offers potential therapeutic avenues (Fig. 2).

PD. PD is the second most prevalent neurodegenerative disorder, succeeding AD, with a primary impact on the elderly population (97). PD is characterized by the subclinical presence of cytoplasmic proteinaceous aggregates, specifically α-synuclein, which congregate to form Lewy bodies (LBs) within the substantia nigra. This process is coupled with a decline in dopaminergic (DA) neurons. The extensive degeneration of these DA neurons results in diminished dopamine levels within the brain, which gives rise to a spectrum of clinical manifestations, encompassing challenges in maintaining posture, the emergence of stationary tremors, a decrease in movement speed (bradykinesia) and the onset of joint stiffness reminiscent of ankylosing arthritis (49). Following the loss of dopamine-producing neurons, there is a subsequent degeneration of other neuronal subtypes, giving rise to symptoms unresponsive to dopamine modulation. These symptoms encompass a spectrum of manifestations, including insomnia, compromised olfactory perception, dysregulation of the autonomic system, pain perception alterations and sensory dysfunction (98). However, the precise pathophysiological mechanisms driving PD have remained elusive. In addition to α-synuclein, there is mounting evidence implicating other genetic mutations such as in *Parkin*, leucine-rich repeat kinase 2 (*LRRK2*) and *DJ-1*, alongside environmental factors (including exogenous neurotoxins, age and diet) as potential contributors to the etiology of PD (99,100). These factors intricately contribute to the processes of neurodegeneration and neuroinflammation stemming from oxidative stress, α-synuclein oligomerization and mitochondrial dysfunction. Notably, it has been observed that α-synuclein is also present on the mitochondrial surface, exerting an impact on mitochondrial structural integrity and functional dynamics (101). Impaired complex I has been found in samples from patients with PD and the introduction of toxins inhibiting complex I has been shown to lead to the loss of dopaminergic cells and the manifestation of Parkinson's disease symptoms (102). Furthermore, the presence of mutations in mtDNA has been identified within neurons of individuals with PD (103). As

a result, mitochondrial dysfunction emerges as a recurring determinant in the context of PD.

The PTEN-induced kinase 1 (PINK1)/Parkin pathway serves a pivotal role in the context of mitochondrial dysfunction and its association with PD. In the current understanding of PD, mutations within the PINK1 (*PARK6*) and Parkin (*PARK2*) genes are thought to be associated with the manifestation of autosomal recessive early-onset PD (104). Research has demonstrated that the PINK1/Parkin pathway participates in the progression of PD by influencing mitochondrial autophagy (102,103,105). While mice lacking PINK1 or Parkin do not exhibit significant PD-related phenotypes, a study has demonstrated that these mice accumulate mtDNA mutations, which consequently promotes inflammation in aged Parkin$^{-/-}$ (also termed 'Mutator') mice. This pathological progression appears to be modulated by STING signaling (106). Furthermore, elevated levels of phosphorylated serine 65 of ubiquitin and PRKN have been observed, which are associated with the phosphorylation of ubiquitin by PINK1 at the outer mitochondrial membrane (OMM), have been identified in postmortem PD brains (107). These investigations substantiate a notable association between neuroinflammation and the activation of the PINK1/Parkin pathway in PD, indicating that mitochondrial autophagy has a pivotal role in averting neuroinflammation within this pathological framework.

The involvement of α-synuclein in perturbing mitochondrial function has been previously substantiated (108). It has been documented that α-synuclein possesses a mitochondrial targeting sequence at its N-terminal region, allowing its localization to the OMM. This localization facilitates interactions with components of the outer membrane receptors, thereby leading to compromised cellular respiration (109). This phenomenon has been observed in models of PD and in post-mortem brain tissue from individuals with PD (108,110). Certain α-synuclein species have the capability to intricately bind with the translocase of outer mitochondrial membrane 20 receptor, contributing to mitochondrial dysfunction and an elevated generation of ROS (108). Notably, a study employed a seeding-based model of α-synuclein fibrillization to validate that the progression of LB formation, beyond mere fibril assembly, is a key catalyst in neurodegeneration, additionally exacerbating mitochondrial impairment and synaptic dysfunction (111). This suggests an intrinsic link between mitochondrial dysfunction, α-synuclein aggregation and the formation of LBs.

LRRK2 is another pivotal gene implicated in mitochondrial dysfunction within the context of PD. This gene exerts its influence by modulating the OMM adaptor protein responsible for orchestrating mitophagy, a critical process in maintaining mitochondrial quality. Consequently, this regulatory role of LRRK2 leads to diminished mitochondrial transport along the intricate cytoskeletal network (112). Consistent findings were observed in neurons from LRRK2 mutant rats (113). Mutant LRRK2 inhibits the recruitment of Parkin to the OMM and its interaction with Drp1, thereby suppressing PINK1/Parkin-mediated autophagy, which leads to impaired segregation and degradation of damaged mitochondria (114).

The NLRP3 inflammasome assumes a pivotal role in instigating the neuroinflammatory cascade observed in PD. Heightened levels of inflammasome constituents and inflammation-associated factors have been discerned within blood samples sourced from individuals with PD (105,115). Mitochondrial impairment within microglia, coupled with the activation of the NLRP3 inflammasome, has been reported in both *in vitro* and *in vivo* models of PD (116). In addition, activation of NLRP3 has been observed in PINK1$^{-/-}$ or Parkin$^{-/-}$ microglia, while inhibitors of the inflammasome can effectively suppress this activation process (117). Furthermore, the attenuation of NLRP3 inflammasome activation not only mitigates neuroinflammation and ameliorates motor impairments but also safeguards against the depletion of DA neurons in both a mPTP-induced PD model and a human α-synuclein overexpression PD model (118).

Collectively, the convergence of α-synuclein oligomerization, genetic mutations, impaired mitochondrial autophagy and NLRP3 activation constitutes a synergistic interplay contributing to mitochondria-associated neuroinflammation during the progression of PD (Fig. 3).

MS. MS is a chronic inflammatory disease of the CNS characterized by demyelination and axonal degeneration (119). The inflammation observed in MS arises from elements of both the innate and adaptive immune systems, encompassing the proliferation and dysregulation of pro-inflammatory T lymphocytes, activation of B cells and secretion of inflammatory cytokines (120). At the onset of MS, pathogenic inflammatory T lymphocytes infiltrate the CNS, triggering an immune response that activates microglia and astrocytes, leading to acute inflammation. Subsequently, B cells are further activated, initiating a cascade that sustains chronic inflammation (121). While anti-inflammatory and immunomodulatory therapies have become mainstream in the treatment of acute demyelinating episodes, options remain limited for addressing the progressive stages of MS (122). Further exploration of the pathogenesis of MS is therefore still required.

A recent study has substantiated that mitochondrial dysfunction contributes to CNS damage in MS (123). Mitochondria function as the principal energy supply units within neurons. Neurons facilitate signal transmission through membrane depolarization, which is facilitated by the electrochemical gradient of Na^+/K^+-ATPase. In the context of MS, the interplay of chronic inflammation and myelin disruption leads to a redistribution of ion channels. The heightened presence of Na^+/K^+-ATPase intensifies ATP consumption (123). At this critical juncture, mitochondria can compensate by augmenting both their quantity and volume, thereby inducing alterations in neuron positioning and morphology (123). Persistent inflammation triggers the activation of macrophages and microglial cells, thereby instigating the release of ROS and inducing oxidative stress (124). This exacerbates the release of glutamate, ultimately culminating in neuronal damage (120). Oxidative stress imposes secondary damage on both mitochondria and macromolecules (such as mtDNA, ETC proteins and lipids), thereby significantly impairing energy generation (120). While nuclear factor erythroid 2-related factor 2 and antioxidant enzymes such as heme oxygenase-1, are activated during periods of hypoxic stress to compensate for mitochondrial dysfunction, once a critical threshold of reduced ATP production is reached, ion homeostasis becomes compromised (125). This disruption results in chronic inflammation and triggers Ca^{2+}-dependent proteases, ultimately leading to apoptosis

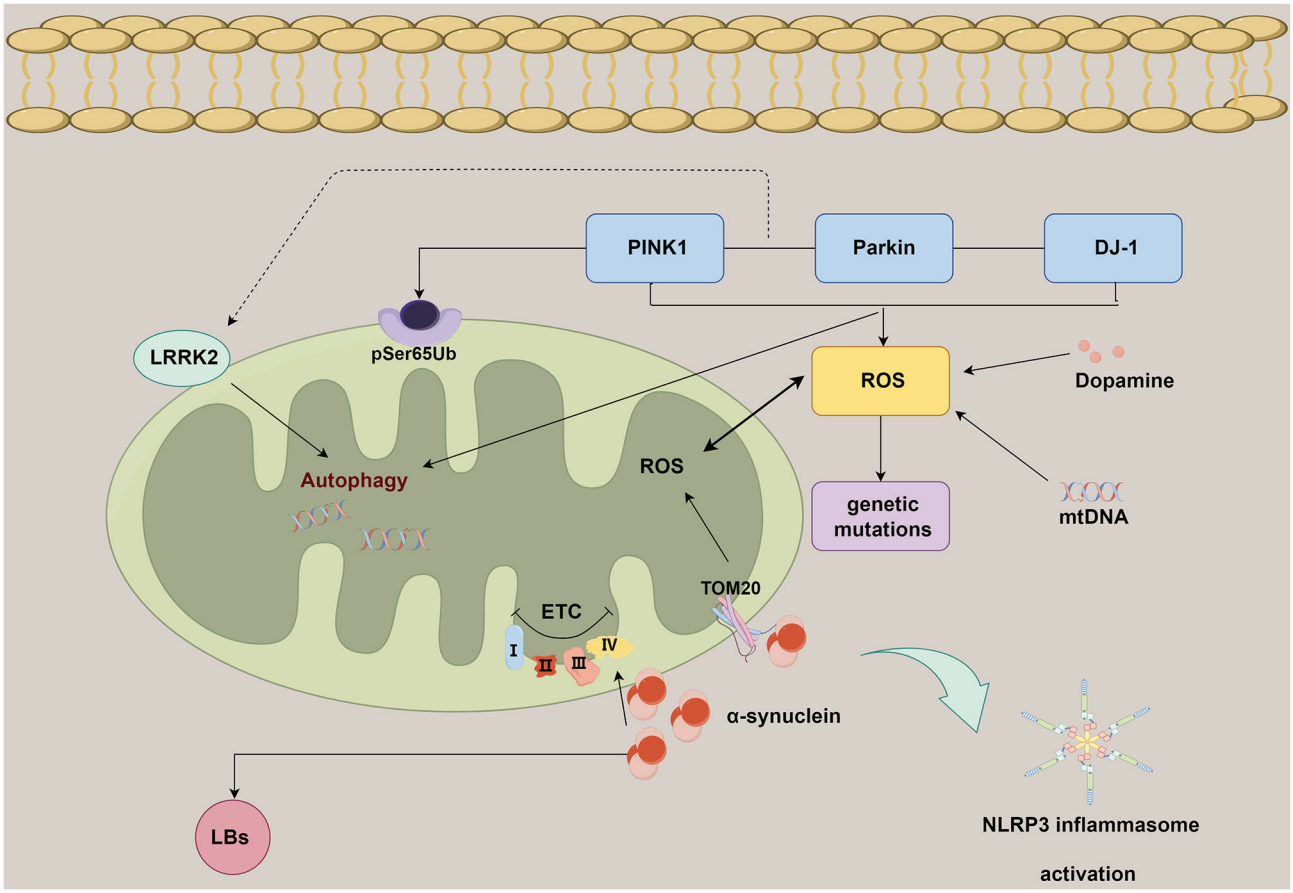

Figure 3. Mitochondrial dysfunction in Parkinson's disease. ROS, reactive oxygen species; mtDNA, mitochondrial DNA; NLRP3, NLR family pyrin domain containing 3; LRRK2, leucine-rich repeat kinase 2; PINK1, PTEN-induced kinase 1; ETC, electron transport chain; TOM20, translocase of outer mitochondrial membrane 20; LBs, Lewy bodies.

within demyelinated axons (126). The presence of oxidized DNA and lipids has been observed in apoptotic oligodendrocytes and dystrophic axons within active MS lesions (127). Furthermore, the inflammatory factor, TNF-α, exacerbates the impairment of OXPHOS through Ca^{2+} modulation (128). The resultant reduction in ATP production hampers the ability of the Na^+/K^+-ATPase to maintain gradients after action potentials, leading to an accumulation of sodium within the neuronal cytoplasm. This phenomenon, in turn, compels Na^+/Ca^{2+}channels to facilitate intracellular calcium transfer, initiating a cascade of Ca^{2+}-dependent apoptosis that ultimately culminates in neuronal death. This intricate process significantly contributes to Wallerian degeneration and irreversible neurofunctional impairment (120). In MS animal models, double-strand breaks in mtDNA lead to chronic demyelination and axonal degeneration, which are exacerbated over time (129). It is noteworthy that mitochondrial dysfunction and oligodendrocyte myelin formation are inherently interconnected. The level of the mitochondrial metabolite, *N*-acetylaspartate (NAA), is reduced in the normal-appearing white matter of patients with MS (130,131). *In vitro* experiments have confirmed that extracellular NAA improves Oli-neuM cell differentiation and axonal connectivity (132). Furthermore, the NLRP3 inflammasome and cyclic GMP-AMP synthase-STING pathway, which are associated with increased mitochondrial damage and respiratory stress, are activated in MS (133,134). These findings highlight the pivotal role of mitochondrial function in the progression of MS (Fig. 4).

Epilepsy. Epilepsy is a persistent neurological condition distinguished by the recurrence of seizures intertwined with an underlying neurodegenerative process (135). The intricate diversity of epilepsy presents a significant challenge for its treatment (136). Moreover, the success rate of antiepileptic drug therapy remains limited, ranging from 30 to 50% (137). Lately, there has been growing interest in the role of oxidative stress and redox dysregulation in epilepsy. Elevated levels of diverse biomarkers associated with oxidative stress and neuroinflammation have been reported in the brains and peripheral tissues of both human patients and animal epilepsy models (138,139). Therefore, anti-inflammatory and antioxidant therapies hold promising therapeutic potential. Administering these treatments shortly before or after the symptomatic onset of epilepsy could effectively hinder the advancement of spontaneous seizures and potentially delay their onset (140). Moreover, it has been demonstrated that IL-4 exerts a neuroprotective effect during epileptogenesis by lowering TNF-α levels and mitigating mitochondrial swelling in a mouse model induced by kaliotoxin (141).

Mitochondrial dysfunction has a pivotal role in the connection between epilepsy and oxidative stress (136). In total, ~40% of individuals with epilepsy exhibit concomitant

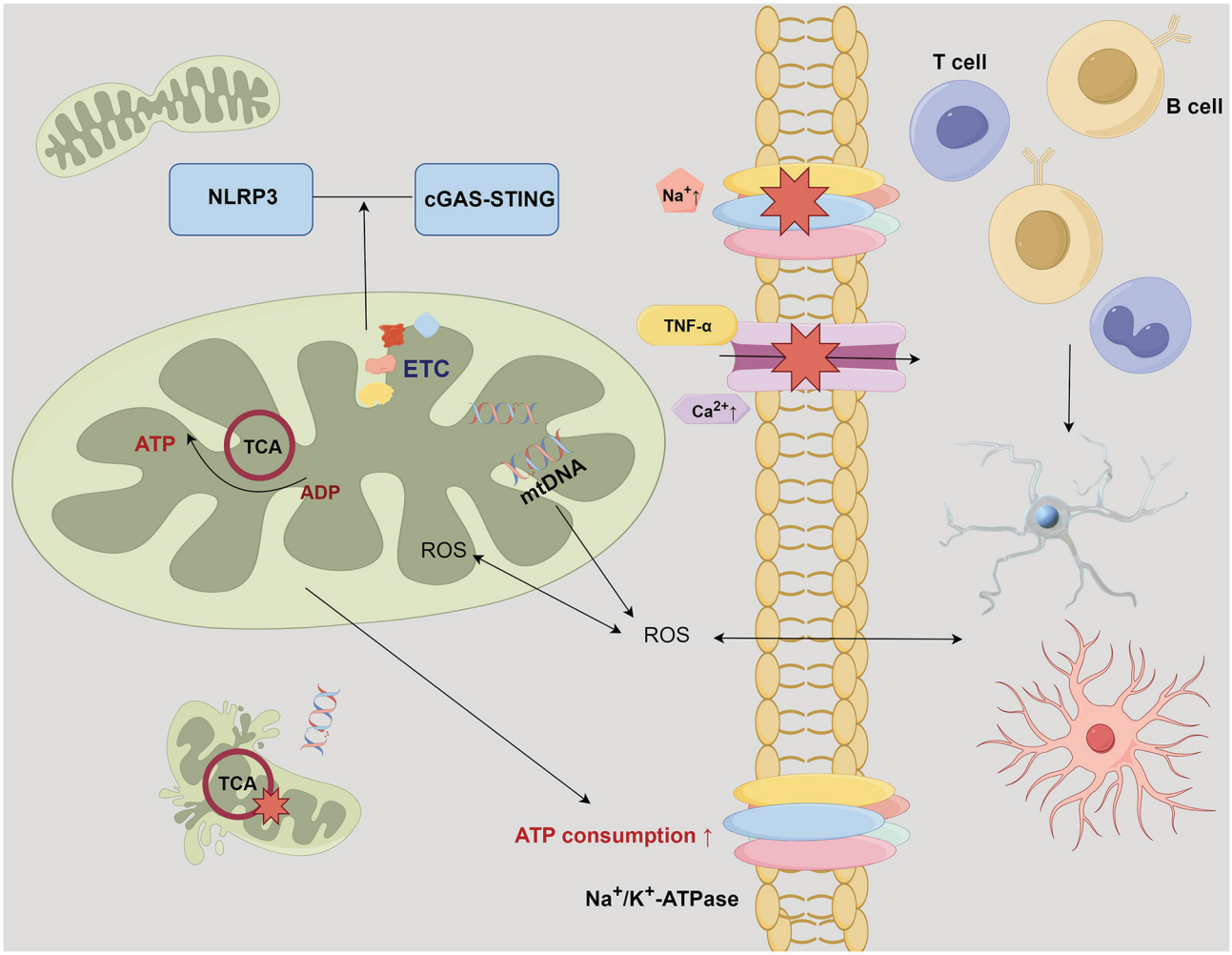

Figure 4. Mitochondrial dysfunction in multiple sclerosis. ROS, reactive oxygen species; ETC, electron transport chain; mtDNA, mitochondrial DNA; TCA, tricarboxylic acid (cycle); NLRP3, NLR family pyrin domain containing 3; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TNF-α, tumor necrosis factor-α.

mitochondrial disorders (142). Mitochondrial dysfunction disrupts the balance of RNS and ROS, resulting in heightened ROS generation, oxidative harm and diminished ATP production. This cascade ultimately culminates in mtDNA mutations and compromised mitochondrial respiration, establishing a detrimental cycle (1,136). Furthermore, there was a notable rise in the occurrence of spontaneous motor seizures within mitochondrial SOD2$^{-/-}$ mice (143). Conditional deletion of SOD2 specifically in the forebrain led to reduced mitochondrial oxygen consumption and the subsequent development of epilepsy in mice (42). An additional study demonstrated that the targeted removal of neuron-specific mitochondrial SOD2 results in a severe and intricate epileptic phenotype (144). Collectively, these findings indicate that mitochondrial oxidative stress is not solely a result of epilepsy but also contributes to its onset.

Additionally, ROS can directly regulate pro-inflammatory molecules, including IL-1β, high mobility group box-1 (HMGB1) and matrix metalloproteinase 9 (136). Pathways related to HMGB1, toll-like receptor 4 (TLR4) and IL-1β/interleukin-1 receptor 1 have therefore emerged as potential targets for epilepsy therapy (145). HMGB1 interacts with TLR4 and functions as a proinflammatory cytokine in the extracellular environment. Research has demonstrated that the translocation of nuclear HMGB1 and active caspase-3 to the mitochondria enhances programmed necrotic cell death in parvalbumin cells and CA1 neurons during status epilepticus (146-148). Furthermore, another study discovered that the levels of glutathione, an essential antioxidant for maintaining mitochondrial integrity, significantly increased following the administration of antioxidant drugs [*N*-acetylcysteine (NAC) and sulforaphane]. Concurrently, this intervention led to a reduction in HMGB1 production within an acquired epilepsy rat model induced by status epilepticus (149,150). The NLRP3 inflammasome is a molecule associated with epilepsy, which can be triggered by ROS (151,152). Furthermore, it has been empirically shown that mtROS function as a secondary messenger, triggering the activation of NLRP3 and its translocation to the mitochondria, thereby facilitating the activation of IL-1β. Consequently, this process elicits a proinflammatory signal in reaction to mitochondrial dysfunction (153,154). The available evidence suggests that activation of the NLRP3 inflammasome can be inhibited by anti-inflammatory and antioxidant therapy, thereby potentially influencing epileptogenesis (155). A previous study also observed upregulated levels of NLRP3 and IL-1β in children diagnosed with febrile seizures (156). It has

also been suggested that NLRP1 and NLRP4 may have roles in the development of epilepsy. Specifically, NLRP1 has been found to be upregulated in patients with temporal lobe epilepsy (TLE) (157). In a TLE rat model, reducing the expression of NLRP1 was shown to decrease the frequency and severity of seizures (158). The sensitivity of domain-containing protein 4 (NLRC4) to mtROS in astrocytes and its association with mitochondrial oxidative stress in neurodegenerative diseases provide insights into the potential mechanism of NLRC4 in epilepsy (159). This highlights the intricate relationship between epilepsy and mitochondrial dysfunction, emphasizing the need to unravel the multifaceted impact of mitochondrial function on brain activity as a potential avenue for epilepsy treatment.

4. Therapies targeting mitochondria

Mitochondrial therapy for neuroinflammation is an emerging field with potential for the treatment of chronic neuroinflammatory diseases (160). Currently, the overall treatment strategy includes restoring normal mitochondrial physiological functions (ATP production) and antioxidant therapy, clearing mitochondria with abnormal functions through mitochondrial autophagy or other mitochondrial stress responses, gene therapy, restoring mitochondrial dynamics and addressing mitochondrial calcium ion balance disorders (55,149,160-162).

Cytokines such as IL-1-β and TNF-α, as well as their receptors, serve a significant role in the development and progression of AD (55). Inhibiting the interaction of these pro-inflammatory factors may therefore be a more effective therapeutic option for AD. For instance, the anti-inflammatory molecule, minocycline, reduces Aβ and τ pathological lesions in an AD rat model by inhibiting pro-inflammatory cytokines in glial cells through the NF-κB signaling pathway (55). Inhibiting inducible NO synthase and cyclooxygenase-2 is also considered to effectively improve neuroinflammation in patients with AD (163). Excessive activation of microglial cells and reduced phagocytic ability leads to increased accumulation of Aβ plaques and τ hyperphosphorylation, exacerbating neuroinflammation (164). Microglial polarization from an M1 state to a neuroprotective M2 state is also a potential target for treatment. GV-971, a sodium oligomannate, modulates gut microbiota amino acid metabolism to reduce the activation of T helper 1 cells, thereby inhibiting M1-type microglia activation, ultimately alleviating neuroinflammation and enhancing cognitive function in AD mice (165). The second-generation tetracycline, minocycline, selectively inhibits the M1 state of microglial cells and exerts anti-neuroinflammatory effects in patients with AD (166). Antioxidants are also extensively researched in drug development. For instance, vitamin E reduces the production of TNF-α and NO, lowering the levels of ROS and IL-6 induced by lipopolysaccharides in microglial cells, thereby providing neuroprotection (167). Polyphenolic compounds such as flavonoids and vitamin C, may help prevent age-related neurodegenerative diseases based on a clinical study (168). Flavonoids, which are found in daily dietary products, promote the survival of neurons in patients with AD by reducing protein oxidation, inhibiting the JNK and p38 pathways and preventing the production of free radicals (168).

Mitochondrial dysfunction is a well-established feature of PD, with defects in mitochondrial complex I activity and increased oxidative stress (169). In response to the characteristics of this disease, the application of the mitochondria-targeted antioxidant, mitoquinone (MitoQ), has been gradually gaining attention. Cell experiments have confirmed that MitoQ can reduce membrane leakage, oxidative stress and apoptosis induced by α-synuclein (170). In fruit flies with *PINK1* knockout, vitamin K2, structurally similar to coenzyme Q10 and also serving as an electron carrier in the ETC, was found to alleviate oxidative stress in PD (162). However, in a double-blind clinical study assessing untreated patients with PD using the Unified Parkinson Disease Rating Scale, it was discovered that PD did not improve after 12 months of MitoQ administration (171). Further research is therefore needed to determine the effectiveness of MitoQ. Niacinamide (Vitamin B3 and NAM) and its derivatives are currently under investigation, with the aim to normalize redox levels (172). NAC has also been reported to have demonstrated antioxidant properties in a clinical trial (173). Additionally, a promising candidate in recent clinical trials is ursodeoxycholic acid (UDCA), known for its broad safety profile and its ability to prevent mitochondrial membrane depolarization and stabilize cytochrome c in mitochondria (174,175). The therapeutic potential of UDCA in treating mitochondrial damage has been demonstrated in $LRRK2^{G2019S}$ mutant PD patients and $LRRK2^{G2019S}$ transgenic flies (161). Mitochondrial autophagy is also a crucial target for PD treatment. In PD cell and mouse models, celastrol plays a neuroprotective role by activating mitochondrial autophagy and inhibiting DA neuron loss (176). Furthermore, mitochondrial dynamics may represent a potential target for PD treatment. A study has confirmed that the mitochondrial fission GTPase Drp1 inhibitor, mdivi-1, can be used to inhibit mitochondrial fragmentation in α-synuclein rat PD models, reducing neurodegeneration and mitochondrial oxidative stress (177). Notably, it has been observed in both animal models and patients with PD that physical exercise can enhance mitochondrial biogenesis, providing new avenues for the treatment of PD (178,179).

The treatment of MS is inherently complex due to the varying subtypes of MS, each requiring distinct therapeutic approaches. While significant progress has been made in the treatment of MS, such as the effectiveness of the anti-CD20 antibody, ocrelizumab, and the sphingosine-1-phosphate receptor (S1PR) modulator, siponimod, in patients with primary progressive MS and relapsing-remitting MS (180,181), the management of other progressive forms of MS remains challenging. For instance, in phase III clinical trials, the S1PR modulator, fingolimod, did not demonstrate a reduction in disability progression in patients with primary progressive MS (182). Immune-modulating compounds, such as siponimod and ocrelizumab, targeting degenerative mechanisms may therefore not comprehensively address neurodegenerative processes. Furthermore, the development of new drugs is hindered by the incomplete understanding of the pathogenesis of progressive MS and the absence of suitable animal models. The onset of MS is often associated with the activation of microglia and the continued involvement of T cells and B cells, which release high levels of ROS and RNS, leading to mitochondrial and axonal damage, and ultimately resulting

in neurodegeneration. Therefore, targeting mitochondria has emerged as a focal point in the elucidation of methods to combat MS. Currently, mitochondrial protective strategies, such as minocycline, iron (Fe^{2+}) chelating compounds and antioxidants that reduce oxidative stress, have shown a certain degree of efficacy in MS treatment (119). Recent research has elucidated that mitochondrial dysfunction impairs Na^+/K^+-ATPase, leading to Na^+/Ca^{2+} exchanger reversal and calcium overload, thereby mediating axonal degeneration (183). Notably, mitochondrial transplantation into the medial forebrain bundle has been shown to ameliorate motor deficits in 6-hydroxydopamine-induced PD rats, enhancing mitochondrial functionality (184). It has also been demonstrated that neural stem cells effectively deliver functional mitochondria to target cells via extracellular vesicles, thereby remedying mitochondrial functional deficits in mice with experimental autoimmune encephalomyelitis (184). These studies therefore provide evidence supporting the potential use of mitochondrial transplantation as a therapeutic strategy for MS in the future.

Mitochondrial dysfunction is one of the most prominent features of epilepsy, affecting 35-60% of patients with epilepsy (185). Previous research has found that cannabidiol (CBD) can reduce the frequency of epileptic seizures (186). This may be related to its ability to induce the formation of mitochondrial-derived vesicles through the PINK1/Parkin pathway, which participates in mitochondrial repair (187). Recent evidence suggests that CBD engages in mitochondrial-related anti-inflammatory and antioxidant activities, where it reverses iron-induced mitochondrial dysfunction by rescuing mitochondrial ferritin and modulating mtDNA epigenetics, and participates in neurodegenerative mechanisms via the NF-κB, phosphorylated p38 MAPK and peroxisome proliferation-activated receptor γ pathways (188). Currently, the Food and Drug Administration has approved the drug compound, Epidiolex, which contains CBD, for the treatment of seizures (189). Furthermore, a study has also found that the IL-1 receptor antagonist, anakinra, can reduce seizure frequency (190). The antiepileptic drug, levetiracetam, can reduce neuronal excitability by restoring the resting membrane potentials of IL-1β-induced neurotoxic astrocytes and promoting the secretion of TGF-β1 (191). Additionally, levetiracetam modulates the opening of the mPTP via synaptic vesicle protein 2A, reducing neural hyperexcitability in patients with AD and AD animal models (192). Other antioxidants targeting mitochondria, such as polyphenols, vitamins and thiols, have been shown to help reduce epileptic seizures (193). Therefore, targeting mitochondria may be a key approach to treating epilepsy.

In general, the treatment strategies for chronic neuroinflammatory diseases remain focused on combating oxidative stress and ameliorating mitochondrial functional impairments, which constitute shared pathophysiological features of such conditions. Mitochondrially-targeted therapy stands out among emerging therapeutic modalities due to its ability to selectively target mitochondria, neutralizing reactive ROS and restoring their functionality. Currently, research on agents such as MitoQ is the most extensive. However, despite demonstrating significant therapeutic effects in animal models, MitoQ has not yielded the anticipated substantial benefits in clinical trials for PD or AD (194,195). Moreover, effectively penetrating the blood-brain barrier and achieving optimal concentrations within target brain tissues remain pressing challenges. Additionally, mitochondrial-targeted therapies fail to selectively recognize damaged mitochondria and cannot directly modulate mitochondrial dynamics and mitophagy processes, which may contribute to their suboptimal clinical efficacy (194). In addition to mitochondrial-targeted therapy, mitochondrial gene therapy is emerging as a novel research domain. Treatment strategies encompass restoring normal mitochondrial function, repairing or eliminating mutated mtDNA and delivering wild-type mtDNA (196). Despite the development of various delivery systems, including mitochondria-targeting peptides and liposomes, as well as physical methods such as electroporation and hydrodynamic injection, effectively delivering therapeutic macromolecules to mitochondria remains a challenge due to the presence of the blood-brain barrier (196). Furthermore, delivery systems may induce cytotoxicity or interact with endogenous biomolecules, leading to aggregation and reduced efficacy (197). The development of mitochondrial genome editing technology is still in its nascent stages, necessitating further understanding of how RNA and editing tools penetrate mammalian mitochondria (198). Efforts to develop more precise and safer mitochondrial-targeted drugs may therefore be a future research focus.

5. Conclusions and future directions

Mitochondrial dysfunction is a common feature of chronic neuroinflammatory diseases and exploring its pathological mechanisms may provide new avenues for future treatments. Various drugs have been developed that target mitochondria, focusing on aspects such as antioxidation, mitochondrial autophagy regulation, calcium ion balance and gene repair. However, clinical application of these drugs remains a significant challenge. Exploring new therapeutic targets, selectively targeting dysfunctional mitochondria, ensuring delivery of drugs across the blood-brain barrier into the brain and minimizing adverse reactions may be the focus of future research. Additionally, advancements in mitochondrial genome editing technology offer hope for the precise manipulation of mitochondrial function and addressing genetic abnormalities in neuroinflammatory diseases.

Future treatment strategies may not be limited to a single approach; combining anti-inflammatory and antioxidative therapy with mitochondrial-targeted treatment may enhance overall treatment safety and efficacy. In conclusion, while mitochondrial-targeted therapy holds promise for the treatment of chronic neuroinflammatory diseases, addressing current limitations is crucial. By overcoming delivery challenges, enhancing treatment specificity and exploring new therapeutic targets, mitochondrial-targeted therapy holds promise for treating chronic neuroinflammatory diseases and other neurological disorders.

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Competing interests

The authors declare that they have no competing interests.

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