REVIEW

Mitochondrial Dysfunction as a Signaling Target for Therapeutic Intervention in Major Neurodegenerative Disease

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Abstract

Neurodegenerative diseases (NDD) are incurable and the most prevalent cognitive and motor disorders of elderly. Mitochondria are essential for a wide range of cellular processes playing a pivotal role in a number of cellular functions like metabolism, intracellular signaling, apoptosis, and immunity. A plethora of evidence indicates the central role of mitochondrial functions in pathogenesis of many aging related NDD. Considering how mitochondria function in neurodegenerative diseases, oxidative stress, and mutations in mtDNA both contribute to aging. Many substantial reports suggested the involvement of numerous contributing factors including, mitochondrial dysfunction, oxidative stress, mitophagy, accumulation of somatic mtDNA mutations, compromised mitochondrial dynamics, and transport within axons in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis. Therapies therefore target fundamental mitochondrial processes such as energy metabolism, free-radical generation, mitochondrial biogenesis, mitochondrial redox state, mitochondrial dynamics, mitochondrial protein synthesis, mitochondrial quality control, and metabolism hold great promise to develop pharmacological based therapies in NDD. By emphasizing the most efficient pharmacological strategies to target dysfunction of mitochondria in the treatment of neurodegenerative diseases, this review serves the scientific community engaged in translational medical science by focusing on the establishment of novel, mitochondria-targeted treatment strategies.

Keywords Mitochondrial dysfunction · Oxidative stress · Mitochondrial quality control · Fusion · Fission · Mitochondrial medicine

Introduction

Neurodegenerative diseases are diverse group of devastating, and incurable condition, defined by the gradual deterioration and death of cells in the central nervous system. These pathological conditions, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS), are distinguished by the gradual loss of neuron cells, impaired motor or cognitive functions, and abnormal accumulation aggregated proteins. An increasing amount of research on NDD shows changes to the brain's reduction–oxidation (redox) equilibrium as well as bioenergetics deficits (Yap et al. 2009).

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The clinical manifestations of neurodegenerative diseases can be widely defined, with pyramidal and extrapyramidal movement abnormalities and cognitive processing impairments is perhaps the most frequent (Amor et al. 2010; Lyman et al. 2014). Few people have homogeneous syndromes, with the majority having a combination of clinical features. Diagnostic precision is crucial because it allows for more accurate prognosis and frequently informs particular care and treatment. But though particular protein accumulates in significant amounts and morphologic vulnerability are closely correlated with neurodegenerative diseases (NDD). Several more underlying principles characterized by a progressive neurological malfunction, such as proteotoxic stress in the ubiquitin and lysosomal systems, reactive oxygen species (ROS), apoptosis, and inflammation, are shared by neurodegenerative diseases (Cenini et al. 2019; Umare et al. 2021).

The cytosolic organelles "mitochondria" is crucial for birth as well as death. Abundant evidence from preclinical and clinical research shows that mitochondria are important in aging, cancer, hyperglycemia, and neurological diseases like Alzheimer's, Huntington's, and Parkinson's disease (Lin and Beal 2006). Mitochondrial malfunction supposed to be a key in the ROS generation, is the fundamental cause of several forms of neurodegenerative illnesses. In neurodegenerative disorders, many evidences suggesting altered mitochondrial architecture and functions, including structure, size, location, and mobility, have appeared recently (Chen et al. 2012; Onyango et al. 2010). Besides looking at neurodegenerative disorders in general, a complete knowledge of mitochondrial activity and their involvement in degeneration might open up new avenues for the management of progressive neurodegenerative diseases. Mitochondria have been identified as critical organelles in the complicated interaction among neurodegeneration since they are both a generator of innate immune signals.

Mitochondrial defensive agents offer a possible novel approach to developing drug compounds that can alter the pathophysiology of neurodegeneration (Moreira et al. 2010). The new finding that mitochondrial dysfunction is at the root of several NDD has given rise to new targeted therapies aimed at preserving/improving mitochondrial function (Missiroli et al. 2020; Umare et al. 2021). Excessive generation of oxygen species by mitochondria, both actively and as a secondary result of all other malfunctions, alteration in energy metabolism, mitochondrial dynamics as well as transport and mutation, are substantial sources of problems in well almost all scenarios in which mitochondrial dysfunction makes a significant contribution to disease. The new revelation that mitochondria seem to be at the crossroads of a cell's death and life, especially through the engagement of mitochondrial dysfunction in plethora of diseases, has created mitochondria an exciting target for new drugs as well as treatment strategies (Blesa et al. 2015; Picca et al. 2021).

Healthy Mitochondria

Mitochondria are versatile organelles which are already inherited from the mother and form clusters in several cells that keeps the intricate balance of fusion, fission, mitochondrial generation, and mitophagy (Ma et al. 2020). Even though mitochondria are primarily known for producing and storing energy from the oxidation of complex molecules under aerobic conditions via oxygen consumption, their numerous anabolic features are largely neglected (Giorgi et al. 2012; Herst et al. 2017). Cellular energy is primarily produced through oxidative phosphorylation inside mitochondria that are essential organelles for many biological processes such as metabolic activities, lipid biogenesis, calcium homeostasis, and programmed cell death (Guzy and Schumacker 2006). Due to the general significant level of ATP production required to maintain neuronal energy demands, oxidation of glucose is the vital energy source in the central nervous system. Since ATP could not be preserved, the mitochondria should produce large quantities of ATP continuously, takes about 25% of the overall volume of the cell (Mergenthaler et al. 2013).

The fundamental mitochondrial function is to transform the byproducts of glucose, polypeptide, and fat oxidation to carbon dioxide and water by employing the electron transport chain's (ETC) essential enzymes of complexes I to IV. Ions (H^+) are pushed out from matrix to the inter-cristae region during such events, forming a gradient of protons. Through complex V, protons moving back along this gradient start to produce ATP. This process of generating ATP with substrate oxidation in the mitochondria is called as oxidative phosphorylation, and is vital for the health of many body tissues (Hall et al. 2012). Because the onset of metabolic complications is usually characterized by a disturbance in mitochondrial activity, malfunction of above complexes of mitochondria could also display an integral role throughout the development of several chronic illnesses (Giorgi et al. 2012; Upaganlawar et al. 2021).

Mitochondria significantly influence several biochemical cell signaling pathways. It can decode a wide range of extracellular inputs into various intracellular responses, spanning from energy generation to cell mortality. The careful regulation of mitochondrial calcium (Ca^{2+}) balance is critical in several activities involving this organelle. Based on the tissues engaged, numerous pathogenic diseases might emerge when mitochondrial Ca^{2+} equilibrium is disrupted. Recent research has given insight on the chemical identities of the key proteins that are

involved in mitochondrial Ca^{2+} trafficking (Calì et al. 2012; Erustes et al. 2021; Giorgi et al. 2012; Loncke et al. 2021; Mitochondrial Ca et al. 2022).

In addition to fulfilling the traditional function of providing the cell with energy, mitochondria actively control innate immune responses to sterile insults and infectious agents (Banoth and Cassel 2018; Missiroli et al. 2020). This can happen in two means: firstly, by direct stimulating the production the immune system response, and subsequently, by modifying a reaction. Direct stimulation is frequently associated with mitochondrial injury or dysfunction, although modulation can be found as a consequence of healthy mitochondrial processes and activities (Banoth and Cassel 2018).

Mitochondria perform important part in cell's apoptotic process activation (Wang and Youle 2009). The stimulation of caspases results in fragmentation and destruction of various cellular components, which is crucial to apoptosis control. Members of Bcl-2 family govern the discharge of proteins from the space between the mitochondrial inner and outer membrane that, once in the cytosol, stimulate caspase proteases which de-stabilize cells and signal effective phagocytosis of cell corpses (Picca et al. 2021; Tsujimoto 1998). Hence, caspase expression must be and is strictly regulated. In humans, mitochondrial pathway has been considered as one of the primary apoptotic routes. It is an important site for the interaction of both antiapoptotic and proapoptotic enzymes which determines cell's fate. Moreover, it is the source of signals that initiate caspase activation via multiple processes and are stimulated by cytotoxic stress (Fulda and Debatin 2006; Vringer and Tait 2019).

What Goes Wrong in Neurodegenerative Disorders

Abundance of reports supports that significance of mitochondrial affliction in the pathological development of neurodegenerative disorders (Chen et al. 2012; Lin and Beal 2006). Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD) are some of the most common of these disorders, and they are all delineated by marked neuronal cells loss, impaired cognitive and motor functions, and an abnormal aggregated proteins accumulation [3,30]. The key risk factor for many human illnesses, including NDD, is aging (Akbar et al. 2016; Balaban et al. 2005; Cadenas and Davies 2000; Umare et al. 2021). A plethora of evidence supports impairments in bioenergetics along with brain's reduction–oxidation (redox) homeostasis alterations with the increasing of the age (Fig. 1). The overall "mitochondrial theory of aging" supports the association of mitochondria in aging and associated disorders like NDD (Cobley et al. 2018; Gandhi and Abramov 2012; Trivedi 2021).

Oxidative Stress

Reactive oxygen species (ROS) production are of biological significance in variety of physiological settings which involves cellular adaptation to hypoxia, immune response, repair processes, synaptic plasticity, differentiation, learning, and memory and cellular survival via mitophagy (Apel and Hirt 2004; Chen et al. 2012). As the brain particularly susceptible to oxidative stress induce injury, overproduction of ROS coupled with reduced antioxidants can aid to

Fig. 1 Mitochondrial dysfunction and associated imbalance in neurodegenerative disorders
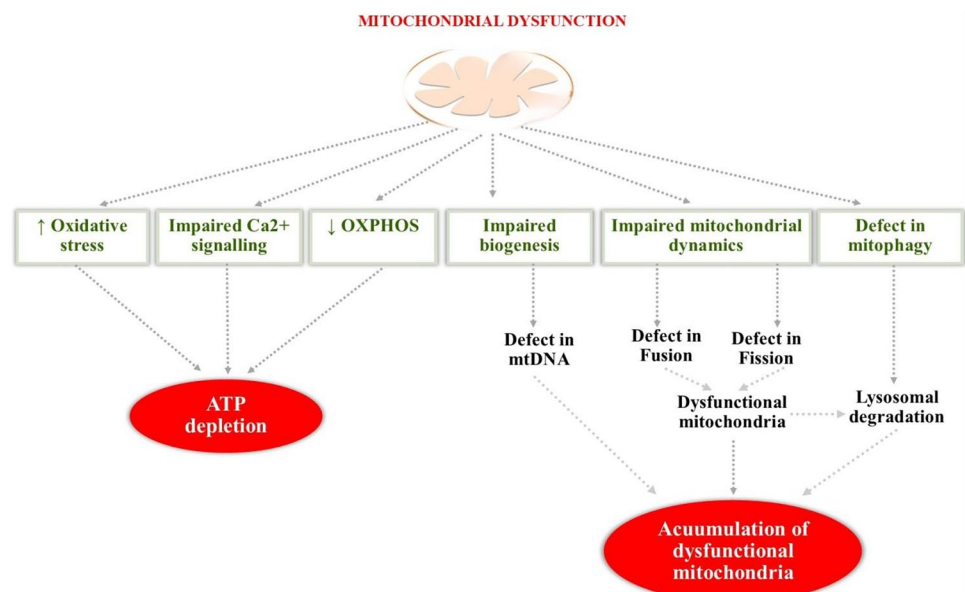
neuronal loss in neurodegeneration (Andersen 2004). ROS-induced damage first target mitochondrial structures, which undergo severe oxidative changes (Marde et al. 2022; Umare et al. 2022; Valko et al. 2007). Oxidative stress can alter the mitochondrial function in many different ways including mtDNA mutations, depressing the functions of the respiratory chain, varying mitochondrial membrane permeability; calcium homeostasis disturbances, and damage antioxidant system, altered mitochondrial permeability eventually causing apoptosis.

Nitrogen and reactive oxygen species are primarily produced by mitochondrial monoamine oxidase (MAO) B and complexes I and III, which are found inside the mitochondria. In PD and AD, a region-dependent modulation of MAO has been observed (Tong et al. 2017). Reduced mitochondrial complex I and III activities have been reported in postmortem AD brain (Cardoso et al. 2004). In PD, deficiency of NADH dehydrogenase and mitochondrial complex I in substantia nigra region has been reported (Gatt et al. 2016). As PD has multifactorial origin, environmental toxicants also play important role in pathologic mechanisms, which includes increased ROS in nigral dopaminergic neurons, oxidative phosphorylation inhibition leading to reduce ATP production, alteration in membrane potential and activation of mitochondrial cytochrome C (Agnihotri and Aruoma 2019). HD mainly involves dysfunctional striatum and cortex, and a decrease in activity of mitochondrial complex II has been reported in patients having HD as well as with injection of 3-nitropropionic acid, an animal models for HD implicating the role of striatal mitochondria in HD (Uddin et al. 2020). According to numerous studies disrupted $Ca2+$ homeostasis in striatal mitochondria was observed in HD mice. Though the involvement of oxidative stress in HD is unclear, the mutant HTT (mHTT) interaction with mitochondria thought to generate ROS mainly through disruption in $Ca2+$ homeostasis, which triggers the mitochondrial permeability transition pore (mPTP), leading to distorted ATP level and aids the release of cytochrome c, thereby further elevating ROS production (Zheng et al. 2018a). Substantial evidence indicates that an excess ROS production in ALS to be associated with an impaired antioxidant defense attributing mitochondrial dysfunction as important pathological feature associated with neurodegeneration in ALS (Cunha-Oliveira et al. 2020).

Mitochondrial Bioenergetics

In the brain, flexibility of metabolic functions rely on the interplay between mitochondrial oxidative phosphorylation systems (OXPHOS) and glycolytic pathways. The mitochondrial OXPHOS uses amino acids, fatty acids, and glucose as substrates to generate reducing equivalents, which are then converted to ATP. On the other hand, elevated levels

of $H2O2$ are thought to mediate the negative consequences connected to mitochondrial dysfunction in NDD since they have been linked to redox alterations in the mitochondria and macromolecule oxidation throughout aging. Glutathione (GSH) or thioredoxin (Trx)-driven enzymes in the brain mitochondria mostly remove $H2O2$ and rely on NADPH as the final electron donor. With regard to NDD, including PD, AD, HD, and ALS, there is overwhelming proof that OXPHOS is altered as a result of the accumulation of misfolded proteins brought on by gene mutations or abnormal protein homeostasis (Kawamata and Manfredi 2018; Marde et al. 2021; Wankhede et al. 2022).

Mitochondrial dysfunction due to failure in bioenergetics has been well reported in AD. The positron emission tomography (PET) confirms altered glucose uptake has been linked with the cognitive impairment in AD. Additional, brain atrophy in AD has been associated with impaired mitochondrial transport (Cunnane et al. 2020). Mutation in AD affects mitochondrial $Ca2+$ signaling and reduces OXPHOS function thereby reducing the further ATP deficit, increased ROS, altered cellular $Ca2+$ homeostasis and reduced protein synthesis (Dematteis et al. 2020). The PET studies of PD brain reported mitochondrial dysfunction in dopaminergic neurons along with reduced glycolysis and mitochondrial complex I activity (Zambon et al. 2019). Additionally, aberrant pyruvate and glucose metabolism has been reported in AD and PD. The accumulation of mtDNA with subsequent reductions in OXPHOS are thought to responsible for neurodegeneration in AD and PD (Area-Gomez et al. 2019). In HD, the mutant Htt impairs axonal transport in the motor neurons and also affects glucose uptake altering the ATP generation, reduced mitochondrial function and oxidative phosphorylation in HD neurons (Cunnane et al. 2020). Numerus studies reported reduction in glycolysis as well as mitochondrial function, impaired pentose phosphate pathway in ALS. Moreover, impaired mitochondrial energetics and in astrocytes has been linked with ALS (Allen et al. 2019; Delic et al. 2018; Tefera et al. 2019).

Mitochondrial Damage and Mutation

Mitochondrial dysfunction, a causal factor of aging, is characterized by abnormal cellular redox generation and excess mitochondrial DNA accumulation (mtDNA). The strong relation between mtDNA mutation as well as the production of ROS is, however, still debatable. The mtDNA is more prone to oxidative damage as compared to nuclear DNA, thus in weak antioxidant defense it gets easily damaged by excess generation of ROS. Also, the mutant mtDNA accumulation may reduce the ETC capabilities, resulting in lower adenosine triphosphate generation and higher ROS production (Cha et al. 2015; Xia et al. 2009). Oxidative damage to mtDNA in the brain changes with increased age and

can result in multiple point mutations. Numerous somatic mtDNA mutations caused by ROS or other processes may aggregate in the nervous system with age and hence have a contribution in aging and NDD, although being uncommon at any one place (Simon et al. 2004).

Mitochondrial genetic malfunction has also been linked to Alzheimer's disease pathogenesis. Damaged DNA lesions caused by ROS are substantially more common in AD tissues. Degraded mtDNA and associated proteins have also been discovered in the brain of AD patients, and the base excision repair (BER) mechanism has been reported to be faulty (Canugovi et al. 2014; Krishnan et al. 2012). Similarly in AD, tends to be characterized by mitochondrial malfunction. Microscopy of AD brain tissues demonstrates structural abnormalities in mitochondria. These alterations are often linked with the overproduction of ROS, a reduction in ATP levels, and increased release of cytochrome c oxidase along with mtDNA into the cytosol, which together aggravate neurotoxicity (Zheng et al. 2018b; Zorov et al. 2014).

Individuals having high levels of mtDNA mutations frequently exhibit significant neurological dysfunction, also with extent of neurodegeneration varied largely depending on the kind of mutation and the mtDNA mutation burden across the brain. The research for mitochondrial malfunction and mtDNA mutations being involved in PD is arguably greatest. The discovery of family versions of the illness reveals that a variety of genetic alterations are related with mitochondria and have roles in ROS damage (Taylor and Turnbull 2005; Upaganlawar et al. 2021). Numerous factors have been associated with dopaminergic neurons degeneration which includes, excess ROS, mtDNA mutations, and mitochondrial mechanisms malfunction. Furthermore, ETC deficit in dopaminergic neurons causes mitochondrial disruption and a reduction in the delivery of new mitochondria to dopaminergic neuron endings in the striatum (Ciccone et al. 2013). Mitochondrial dysfunction has also been linked with the pathogenesis of Huntington's disease (HD), with mitochondrial biochemical deficiencies and impaired mitochondrial enzyme activity being observed in HD patients. Huntingtin mHtt or polyQ segments can also cause mitochondrial malfunction. Moreover, investigations have shown that mutated Htt associated ROS targets mtDNA predominantly, which might contribute to mitochondrial change. Also, studies suggested APE1, an BER enzyme is a key target in the preservation of mitochondrial function in HD (Choo et al. 2004; Jimenez-Sanchez et al. 2017; Walker 2007). Also, it has already been postulated that somatic mtDNA mutations might perform a part in the development of a range of distinct neurological illnesses. Elevated concentrations of mutations have been associated with amyotrophic lateral sclerosis, multiple sclerosis, and even neurodevelopmental disorders (Campbell and MacQueen 2006; Simon et al. 2004).

Mitochondrial Quality Control

The cell has mitochondrial quality control (MQC) system responsible for overcoming the defects in the mitochondria. It includes processes such as mitochondrial biogenesis, mitochondrial proteostasis mitochondrial dynamics as well as mitophagy (Fig. 2) (Anzell et al. 2017). MQC represents the equilibrium between the rate of biogenesis and degradation (Dominy and Puigserver 2013). The combination of these mechanisms demonstrates mitochondrial quality control, particularly crucial in cellular illnesses ranging from basic mitochondrial hereditary defects to secondary mitochondrial diseases such as neurodegenerative, inflammatory diseases (Chang et al. 2020; Criscuolo et al. 2021; Suliman and Piantadosi 2015). MQC processes play a crucial part in regulating mitochondrial structure and activity. MQC is made up of three primary components: the mitochondrial dynamics, ubiquitin–proteasome system (UPS), and mitophagy. The UPS system has the ability to modulate the levels of proteins associated with mitochondrial dynamics and death receptors. The UPS is broadly active during perkin-dependent mitophagy and plays crucial roles. Mitophagy is heavily influenced by mitochondrial dynamics (Palikaras and Tavernarakis 2012; Suen et al. 2008; Wei et al. 2015). Thus, abnormal MQC can be important mechanism pathogenesis of the origination and progression of neurodegenerative diseases, making it an important therapeutic target (Wang et al. 2021b; Yan et al. 2020).

Impaired Mitochondrial Biogenesis

Cell triggers mitochondrial biogenesis as a result of increased demand and is regulated via several signaling pathways in response to stimulus. The peroxisome proliferator-activated receptor–gamma coactivator 1 alpha (PGC-1α) regulates the mitochondrial biogenesis; along with numerus transcription factors, includes nuclear respiratory factor (NRF-1/2) and peroxisome proliferator activated receptors (PPARs). The activation of NRF-1/2 pathway via PGC-1α stimulates transcription factor A (TFAM) and other proteins expression [31–32]. The activation of PGC-1α is also associated with high energy consumption and uptake. Another protein AMPK, AMP-activated protein kinase deals with mitochondrial biogenesis. Oxidative stress affects activation of AMPK thereby disturbing mitochondrial biogenesis. AMPK activation also stimulates PGC- 1α pathway, thereby improves biogenesis through PGC-1α-NRF-2 pathway (Fig. 2) (Elfawy and Das 2019). Thus, the proteins involved in mitochondrial biogenesis can also act as therapeutic targets for neurodegenerative diseases. Potential role of PPARγ-PGC1α-NRF2 in the initiation and maintenance of mitochondrial biogenesis makes it a potential target and strategies targeting PPARγ-PGC1α-NRF2 signaling plays
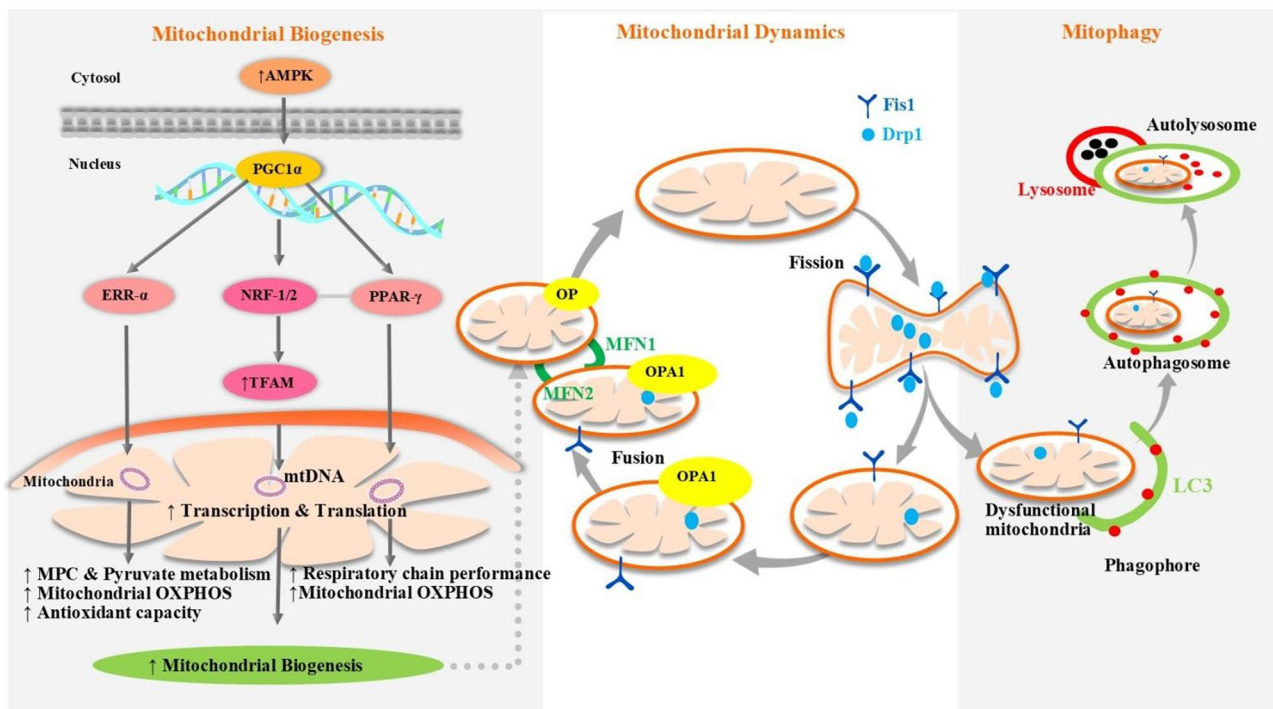
Fig. 2 Mitochondrial quality control (MQC) system. (AMPK) AMP-activated protein kinase, (PGC1α) Peroxisome proliferator-activated receptor–gamma coactivator 1 alpha; (NRF-1/2) nuclear respiratory factor ½; (ERR-α) estrogen-related receptor-alpha; (PPAR-γ) peroxisome proliferator activated receptors; (TFAM) transcription factor A; (mtDNA) mitochondrial DNA, (MPC) mitochondrial pyruvate carrier, (OXPHOS) oxidative phosphorylation system, (Fis1) mitochondrial fission protein 1, dynamin-related protein 1(Drp1), optic atrophy protein 1(OPA1), (MFN2) mitofusin 2, (LC3) micro-tubule-associated proteins 1A/1B light chain 3. MQC system ensures the mitochondrial homeostasis via biogenesis of mitochondria, its dynamics and mitophagy. Through the appropriate stimuli or AMPK triggers the different transcription factors such as PGC1α and TFAM via PGC1α-ERR-α or PPAR-γ-PGC1α-NRF1/2 pathway. TFAM reaches MTDNA through mitochondrial import machinery and upregulates expression of different genes involved in mitochondrial biogenesis and dynamics. Mitochondrial components are ultimately recycled through a specialized pathway, mitophagy

promising role in developing newer treatment for NDD (Jamwal et al. 2021).

Number of studies reported reduced level of PGC-1 in neurodegenerative conditions like AD, PD, and HD, whereas overexpression of molecule was found to exert neuroprotection in disease models, some conflicting reports also suggested deleterious effect associated with PGC-1 overexpression in dopaminergic neurons (Ciron et al. 2012; Jones et al. 2012). The relative number of mitochondria was found to reduce in HD brains, along with PGC-1 and TFAM (Kim et al. 2010). Furthermore, neurodegenerative lesions in the striatum was seen in PGC-1 null mice model of HD (Lin et al. 2004; Oliveira 2010). In AD patients, the low number of mitochondria along with reduced expression of PGC-1, NRF1, NRF2, and TFAM (Calkins et al. 2011; Hirai et al. 2001; Sheng et al. 2012). Both the levels of PGC-1 and NRF-1 were declined in brain region associated with PD. Additionally, PGC-1 polymorphisms have been associated with PD and HD (Che et al. 2011; Clark et al. 2011; Shin et al. 2011; Weydt et al. 2009). In PD, reduced neurogenesis has been associated with the loss of PARKIN,

which directly linked with the downregulation of expression of PGC-1 in basal ganglia (Wang et al. 2021b).

Impaired Mitochondrial Dynamics

Mitochondria are structured in a dynamically changing matrix that undergoes continual fusion and fission in necessary to undertake their activities in the most efficient manner continuously. The processes of fission and fusion of mitochondria are crucial in the formation of new as well as the removal of defective mitochondria. Mitochondria create a densely linked tubular network all across the cell, which encompasses mitochondrial segments constantly breaking away and fusing (Walker et al. 2020; Youle and van der Bliek 2012a, b) (Fig. 2).

The process of fission results in the mitochondrial fragmentation followed by its elimination via mitophagy. (Burman et al. 2017; Frank et al. 2012; Scott and Youle 2010). Several mitochondrial proteins are involved in fission process including mitochondrial fission protein and factor (Fis1 & Mff), GTPase dynamin-related protein 1 (Drp1) and mitochondrial dynamics

of 51 kDa protein (MiD51) (Youle and Van Der Bliek 2012a, b; Zhang et al. 2016). Fis1, is an OMM protein which act as receptor for Drp1. Normally Drp1 binds to Fis1 at tetratrico-peptide repeat (TPR) present on cytosolic side leads to constriction of mitochondrial outer membrane resembling like ring (Gomes and Scorrano 2008; Panchal and Tiwari 2019; Youle and Van Der Bliek 2012a, b). Oligomerization of Drp1 and subsequent binding with GTP hydrolysis is necessary step in mitochondrial fission. Thus, hyperactivation of Drp1 may lead to mitochondrial fragmentation leading to neuronal death (Feng et al. 2020; Manor et al. 2015). The high rate of fission can hinders the elimination rate of impaired mitochondria; thus, it gets accumulated affecting ETC activity and thereby energy production (Twig et al. 2008). In fusion mitochondria merged to each other in order to preserve mitochondrion for survival and growth during embryonic development (Chen 2011). Different proteins that carry out mitochondrial fusion process are Mitofusin 1, 2 (Mfn1&2), on OMM and Optic Atrophy (Opa1) protein, IMM (Panchal and Tiwari 2019). Numerous studies have stated that altered Mfn2 and Drp1 expression are involved in different NDs pathologies (Fig. 3) (Chen et al. 2003; Gao et al. 2017).

Disrupted mitochondrial fusion and fission have been implicated as major pathogenic components supporting a variety of neurodegenerative diseases pediatric and older people. Because mitochondrial activities are vital, severe mitochondrial fission causes brain malfunction. The buildup of alpha-synuclein and tau in the brains of individuals suffering from neurodegenerative illnesses has also been

associated to the impaired mitochondrial fission function. Numerous studies have reported upregulation of fission-related genes such as Drp1 and Fis1, which interact with amyloid-β and tau protein results in fragmentation of mitochondrial in AD (Kandimalla and Reddy 2016).

Increased ROS production one of the target for ROS is regulators of fission proteins thus hampers mitochondrial dynamics in AD (Wang et al. 2008). The Appl gene reported to enhance the fusion process thereby indirectly affecting axonal transport resulting in neuronal loss in AD. Additionally, tau has also been associated with mitochondrial dynamics by interacting with Drp1 (DuBoff et al. 2012; Manczak and Reddy 2012). The mitochondrial dynamics are also controlled by LRRK2 thus its overexpression can lead to increase expression of fission protein resulting in mitochondrial fragmentation (Westermann 2012; Yang et al. 2014). Another ALS gene, TAF15 expression can affect the mitochondrial dynamics, enhancing mitochondrial fragmentation (Altanbyek et al. 2016).

Mitophagy

Mitophagy was initially presented in the research world in 2005 to define a cellular complex process that involves selective sequestering and destruction of old or damaged mitochondria. Under body's normal settings, mitochondria use mitophagy to supply critical macromolecular components for cells and defend against both neurodegeneration and the buildup of defective mitochondria (Chen and Chan 2009;

Fig. 3 Imbalance in mitochondrial dynamics leading to mitochondrial fragmentation
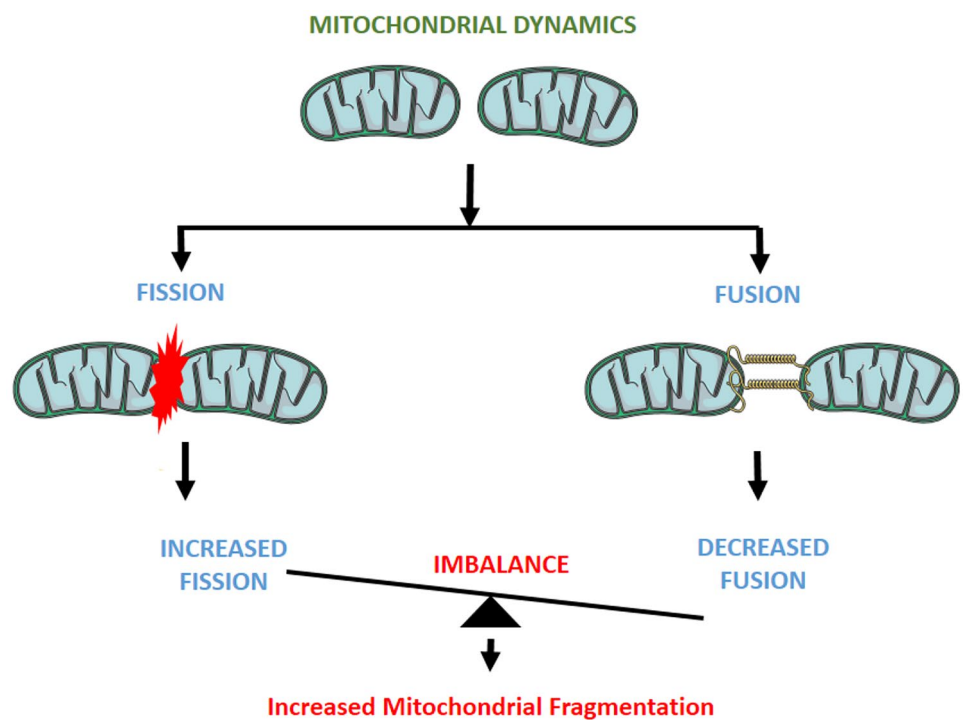
Palikaras and Tavernarakis 2012; Rodolfo et al. 2018). The aggregation of defective and malfunctioning mitochondria has also been described as an early sign that contributes to various neurodegenerative diseases. Under physiological setting the dysfunctional mitochondria has been selected through fission for fragmentation, then degraded in lysosomes. Mitophagy declines with age which further results in an accumulation of dysfunctional mitochondria (Wang et al. 2019).

Mitochondrial malfunction in these disorders generates bioenergetic shortage, cellular calcium disequilibrium, and excessive ROS production, worsening the effects of Amyloid and tau abnormalities and contributing to synaptic dysfunction, cognitive deficits, and impaired memory (Chakravorty et al. 2019). Reduced function and efficiency of mitochondria in CNS, especially in the hippocampus, are linked to aging process and a variety of neurodegenerative illnesses that impair cognition. Moreover, synaptic and intellectual impairment are heterogeneous, accumulating evidences shows that mitochondria are crucial in all these pathways but also that preserving mitochondrial activity may help to avoid age-related and neuronal changes (Guo et al. 2017).

Defective mitophagy has been found in the neurodegenerative patients, which has been mainly linked with the disease-related genes (Wang et al. 2021a). Several pathways are involved in mitochondria targeted degradation via autophagosome, among which PTEN-induced putative kinase protein 1 (PINK1)/cytosolic E3 ubiquitin ligase PARKIN has been the most explored pathway for mitochondrial homeostasis in neurodegenerative diseases. Similarly, their dysfunction has been involved in the development of various disorders. Previous research has concentrated on the interaction between genes such as PINK1, Parkin, α-synuclein, LRRK2, and DJ-1 with mitophagy. The mitophagy has been directly or indirectly linked with PD, as it controls the calcium imbalance, oxidative stress and cell apoptosis via different mechanism (Wang et al. 2022a, 2021a). PD is frequently caused by mutations in the cytoprotective PINK-Parkin pathway. Furthermore, through collaborating with PINK-Parkin pathway, Drp1 is transported to the OMM, resulting in mitochondrial disruption and thereby increasing mitophagy (Ma et al. 2020; Picca et al. 2021). Also, the Drp1 defect has been associated upstream membrane depolarization and ROS production, thereby impairing mitophagy in PD (Feng et al. 2020). A higher rate of apoptosis has been associated with α-synuclein and its mutant forms, A53T α-synuclein, which suggests its involvement in mitochondrial apoptotic pathway. Another protein parkin is associated with the mitochondria, which prevents cell death by inhibiting cytochrome c release and caspase. Also, patients with parkin mutations shows selective impairment in mitochondrial complex I activity (Federico et al. 2012).

A growing body of evidences shows the involvement of α-synuclein in mitochondrial dynamics and mitophagy. In native form the α-synuclein promotes the fission while inhibits mitochondrial fusion, via interactive with Mfn 1/2 and Opa1. Under the pathological state, aggregation of α-synuclein in mitochondrial reduces activity of complex1 while promotes ROS production and impairs mitophagy (Feng et al. 2021a; Risiglione et al. 2021).

Though involvement of autophagy in HD is poorly understood, the impairment in fission/fusion has been reported in few studies. The Huntington protein Htt has been linked with mitophagy as it link the UNC-51-like kinase-1 (ULK1) and sequestosome 1 (SQSTM1/p62), supporting the mutation in Htt may lead to degeneration (Rui et al. 2015). In ALS, the localization of mSOD1 in the mitochondria activation cytochrome c with subsequent release of caspase and may contribute to apoptotic death (Takeuchi et al. 2016).

Mitochondrial Transport within Axons

Mitochondria have several important functions in adult neurogenesis. Their complicated neuronal movement patterns are distinguished by repeated directional changes. The movement can be anterograde or retrograde between cell body and axon in the direction of microtubules and is mediated by certain proteins which includes, kinesin motor protein, dynein motor protein, mitochondrial Rho GTPase (Miro) and Gamma-aminobutyric acid receptor-interacting factor-1/Trafficking kinesin-binding protein-2 (GRIF-1/TRAK2) (Mishra and Chan 2014). Moving mitochondria can be fixed or stall in places with significant metabolism, then move quickly again in accordance to metabolic responses. For the mitochondrial transport Miro attaches to the motor proteins through GRIF-1/TRAK2, followed by kinesin motor protein and dynein helps in the linking mitochondria and microtubule for the transport. Miro is important part of the axonal transport as it maintenance the mitochondrial motility at physiological $Ca2+$ concentration. Thus, the onset of neurodegenerative conditions can be due to energy deficiency at synapses because of improper transport between mitochondria and microtubules (Panchal and Tiwari 2019). Impairment in mitochondrial mobility have been associated with numerous major neurological conditions (Sheng and Cai 2012). During persistent neuronal excitability, mitochondria are frequently preserved in presynaptic terminals and postsynaptic dendritic spines(Li et al. 2004). Axonal transport abnormalities were identified as an initial pathogenic characteristic in a number of neurodegenerative disorders. Dynein-mediated alteration and ultimately affecting axonal transport in neurodegenerative diseases is correlated with dynein cytoplasmic 1 heavy chain 1 (DYNC1H1) and dynactin-1 (DCTN1) mutations. In AD, hyperphosphorylated of tau results in its detachment from microtubule resulting in

microtubule destabilization and thus impairs axonal transport (Cunha-Oliveira et al. 2020). Amyloid precursor protein (Appl gene) in AD binds with kinesin protein and dynein motor protein which are associated with mitochondrial transport (Lin et al. 2017). Thus its overexpression can affect mitochondrial transport directly by reducing function of kinesin heavy chain (KHC) or indirectly via Tau protein (Wang et al. 2020). Other genes that are associated with the axonal transport include PINK 1 and Parkin. Evidences has revealed that PINK1 and Parkin-mediated phosphorylation of Miro protein arrest the process of axonal transport process (Lin et al. 2017). Additionally, α-synuclein and LRRK2 gene mutaion found to affect the mitochondrial axonal transport by altering microtubule stability (Melo et al. 2018; Sleigh et al. 2019). In HD, mutant Htt overexpression has been also associated with impaired mitochondrial axonal transport and mislocalization (Yang et al. 2021). Axonal transport disease linked to microtubules and neurofilaments is seen in a wide range of neurodegenerative conditions. Mutations in SOD1, one of several genes responsible for ALS, produce neurofilament phosphorylation as well as aggregation and an absence of motor complex formation in early cortical neurons (Guo et al. 2020). Furthermore, mutant TDP-43 expression in ALS impairs the axonal transport (Yang et al. 2021).

Targets for Developing Mitochondrial Medicine

Although some of the underlying processes for the neurodegenerative illnesses are unique to each one and eventually result in the degeneration of a particular subgroup of neurons, they all have similar degenerative characteristics, such as mitochondrial dysfunction(Gao et al. 2017). When mitochondrial homeostasis is negatively affected, pathologies like NDD arise which is a result of secondary mitochondrial dysfunctions (SMD). Defects in mitochondrial energy metabolism, dynamics, biogenesis, quality control etc. are major cause of SMD in NDD. There are only palliative treatments available for NDs right now (Table 1). More research is being done to develop medicines that specifically target mitochondria. There have been extensive efforts made in the creation of pharmacological techniques to reinstate mitochondrial integrity because of the wide range of disorders associated with mitochondrial dysfunction. This section will provide the most promising therapeutic targets (Umare et al. 2021; Upaganlawar et al. 2022).

Targeting Free-Radical Generation

For the normal functioning of the CNS, chemical integrity of brain is utmost important. Due to high oxygen requirement and lipid content, make the brain more prone to oxidative stress. Numerous neurodegenerative disorders like AD,

PD, HD, and ALS are the result of biochemical changes due to excessive ROS production. Targeting mitochondrial ROS production is major strategy for the treatment of NDD(Onyango et al. 2010; Umare et al. 2021; Wankhede et al. 2022).

Antioxidants

To counteract the ROS protecting neuron cells and prevents neurodegenerative illnesses, a variety of neuroprotective treatments have been created to date. Specifically, these drugs are antioxidants which exert neuroprotective action by decreasing the oxidative stress and improvement in the overall mitochondrial health. These agents include Olanzapine, Melatonin, Z-LEHDFMK Mitoquinone, Riluzole, Dichloroacetate, Clozapine, N-acetylcysteine, Olesoxime, erythropoietin, vitamin E, Z-FA-MK and Cholest-4-en-3-one, which are extensively studied for their neuroprotective potential (Upaganlawar et al. 2021; Wu et al. 2019). Among these erythropoietin was found to be most promising agent which employ its action by regulating of oxygen balance, glycolysis and mitochondrial dynamics (Aliev et al. 2003; Rey et al. 2021). Several other antioxidants for instance coenzyme Q10, creatine and dimebon, exerts positive action in the AD and PD in preclinical studies, however, some were unsuccessful in the clinical trials (Reddy 2009; Wang et al. 2019).

The small peptide containing-tyrosine (SS-02 and SS-31) are reported as potent antioxidant in preventing oxidative neuronal death (Szeto 2008). These SS peptides act directly on mitochondrial inner membrane. The data from animal studies showed that SS02 and SS-31 readily penetrates the BBB and eliminate free radical in tert butyhydroperoxide (tBHP) mediated ROS generation in cell cultures (Szeto 2006). Evidences also have demonstrated effectiveness of these peptides in PD and ALS (Petri et al. 2006; Xiong et al. 2012).

Targeting Mitochondrial Bioenergetics

The modification of the redox state of mitochondria may serve as an alternate approach for treatment of NDD. There is a mounting body of evidence demonstrated that a diverse mitochondria-mediated signaling cascade is triggered by the mild inhibition of the OXPHOS complexes and enhances various pathways. Complex I inhibition aims to promote healthy aging, postpone the onset of neurodegenerative disease, and provide relief for a number of NDDs, such as AD, HD, PD, and AML. A growing body of evidence supports strong therapeutic potential of nicotinamide riboside, a precursor of NAD +, to prevent cognitive decline, synapse loss, and neuronal death. Additionally, pyruvate improves brain energetics via pyruvate dehydrogenase (Cerutti et al. 2014; Lautrup et al. 2019; Linnane et al. 1992).

Table 1 Therapeutic interventions for mitochondrial dysfunction in neurodegenerative diseases

Tested treatment for mitochondrial dysfunction	Comment	References
Antioxidants-Coenzyme Q10 Idebenone Mitoquinone Carnosic acid Mangiferin	Reduce oxidative stress- provide neuroprotection	(Jaber et al. 2020; Orsucci et al. 2011; Reddy 2009; Wang et al. 2019, 2022b; Wu et al. 2019)
Metformin	Partial complex I inhibitor	(Gueguen et al. 2015; Rotermund et al. 2018; Trushina et al. 2022)
Resveratrol	Partial complex I inhibitor	
Berberine	Partial complex I inhibitor	
Epigallocatechin 3-gallate	Partial complex I inhibitor	
CP2	Partial complex I inhibitor, Activation of AMPK pathway	
MSDC-0160	Block MPC-1,↓mTOR	(Mallet et al. 2022) (Ghosh et al. 2016)
	MPC-1, preserve energy metabolism, neuroprotection & antiinflammatory (↓mTOR)	
Lapatinib ditosylate (LAP)	↓ MPC-1, ↓ ERR-α, antiinflammatory & neuroprotection	(Huang et al. 2020; Salomone et al. 2012)
Pioglitazone	↑ Mitochondrial biogenesis	(Heneka et al. 2015; Huang et al. 2020; Investigators 2015; Salomone et al. 2012)
Thiazolidinediones	PPAR activation	(Cheng et al. 2015)
Resveratrol	↑ AMPK activation	(Vingtdeux et al. 2010)
	↓ Drp1, imporves Parkin & PINK translation	(Li et al. 2019)
	↑ LC3-II, antioxidant	
	↑PGC-1α, ↑TFAM	(Blanchet et al. 2008; Ho et al. 2010; Kim et al. 2007; Whitaker et al. 2016)
	↑Sirtuins, ↑AMPK pathway	(Cantó and Auwerx 2009)
	Partial complex I inhibitor	(Gueguen et al. 2015)
AICAR	↑AMPK pathway	(Vingtdeux et al. 2010)
Melatonin	↑PGC-1α, restore mitochondrial structure	(Tiwari et al. 2021)
LY344864	↑PGC-1α	(Scholpa et al. 2018)
Quinazolinone	Mdivi-1 inhibitor ↓ DRP1 GTPase activity ↓Mitochondrial fragmentation	(Cheng et al. 2015; Gan et al. 2014; Heneka et al. 2015; Risner et al. 2006; Watson et al. 2005)
Rosiglitazone	↑ATP production	(Cheng et al. 2015; Heneka et al. 2015; Quintanilla et al. 2008; Risner et al. 2006; Watson et al. 2005)
	↑PPAR-PGC-1	(Quintanilla et al. 2008)
	↑Protein synthesis	
Bezafibrate	↑PPAR-PGC-1	(Quintanilla et al. 2008)
	↑Protein synthesis	
REN001	↑PPAR-PGC-1	
STACs	↑PGC-1α, AMPK & Sirt1	(Tufekci et al. 2011)
NBMs	↑Sirt1 activation	(Orsucci et al. 2011)
Quercetin	Antioxidant	(Kale et al. 2021; Khan et al. 2018; Liu et al. 2020; Sandhir and Mehrotra 2013; Tiwari et al. 2021)
	↑AMPK & Sirt1	(Tufekci et al. 2011)
Icariin	↓ Mitosis triggered by ROS	(Kale et al. 2021; Liu et al. 2020; Tiwari et al. 2021)
Triterpenoids	↑ NrF2 signaling	(Tufekci et al. 2011)
Mangiferin	Anti-inflammatory, ↓TNF-α, ↓NF-κB, ↓ activation of microglia and astrocytes, Antiapoptotic-↓ caspase activation, ↓ DRP1 activity	(Feng et al. 2019; Wang et al. 2022b)

OXPHOS Modulators

A number of evidence of mitochondrial alterations specifically, OXPHOS defects have been illustrated which results in neurodegenerative diseases (Kawamata and Manfredi 2018). Some agents act as OXPHOS modulators which employ their function through interacting with components of respiratory chain. Coenzyme Q10, an electron carrier in the ETC with antioxidant properties, extensively used for management of disorders associated with mitochondria. In addition, several neurogenic/neurodegenerative illnesses have been treated using coenzyme Q10 with its equivalents, idebenone and mitoquinone. Idebenone act by transferring of electrons from respiratory complex II to III (Orsucci et al. 2011). It has been investigated in various clinical studies for a range of mitochondria associated illnesses because of its antioxidant characteristics and safety profile(Paudel et al. 2020; Singh et al. 2021). Despite its clinical effectiveness in dealing with the Leber's hereditary optic neuropathy (LHON), a Complex I disease, it has been less successful in clinical trials for other neurodegenerative diseases. This may be due to lack of neuronal NAD(P)H: quinone oxidoreductase 1 (NQO1) activity which has contributed to the limited efficacy of idebenone in neurodegenerative disease treatment. Reports conferred that carnosic acid–idebenone combination treatment promoted NQO1-dependent complex I bypass activity in neurons, as well as other brain cell types. This may be able to expose the neuroprotective therapeutic potential of idebenone or related quinones (Jaber et al. 2020).

Complex I Inhibitors

Inhibiting complex I partially with various small molecules, being studied in clinical trials has been used as a cutting-edge treatment NDD. In a small number of clinical trials, metformin, berberine, epigallocatechin-3-gallate, and resveratrol were tested for neurodegenerative illnesses (Rotermund et al. 2018; Wankhede et al. 2022). Another molecule that targets complex 1 resveratrol, it binds the mitochondrial complex 1 and shows pro- and antioxidant effects depending on dose (Gueguen et al. 2015). Recent study reported that, in AD partial inhibition of mitochondrial complex I with the small molecule compound CP2 triggers a variety of AMPK pathways that provide neuroprotection (Trushina et al. 2022). On contrary, complex I is also a significant cause for ROS production. Evidences revealed that inhibition of mitochondria complex I is a major cause of PD in drug abusers. Also the administration of rotenone found to mimic clinical features of PD in animals via complex-I inhibition thereby enhancing oxidative stress in nigral-striatal system (Xiong et al. 2012).

Mitochondrial Pyruvate Carrier

The mitochondrial pyruvate carrier (MPC) is another potential mitochondrial target for the treatment of NDD. The high amounts of energy needed for neural transmission are typically produced by oxidative phosphorylation in neurons, but other regions of the brain, comprising the parietal region and prefrontal cortices, were discovered to primarily rely on aerobic glycolysis. Because of this, the MPC in general play a crucial function in neurons. In these cells, pyruvate is mostly produced by glycolysis, while LDH may also convert lactate to pyruvate. The astrocyte-neuron shuttle is the primary source for lactate which is taken up by neurons from astrocytes. (Bélanger et al. 2011). Abundance of reports supports pharmacological MPC inhibition has been explored as a potential target for NDDs (Fig. 4) (Quansah et al. 2018; Zangari et al. 2020).

The MSDC-0160 analog of MSDC-0602 K is being studied for treatments of AD and PD. The degeneration of hippocampal neurons in AD rat model has been thought to be ameliorated by blocking the MPC-1, which reduces the activation of the mammalian target of rapamycin (mTOR). In D-galactose/ovariectomized rats, an anti-cancer medication, lapatinib ditosylate (LAP), suppresses MPC-1 via decreasing estrogen-related receptor-alpha (ERR-alpha). According to a study, LAP plays an neuroprotective and anti-inflammatory role in the AD that targets MPC-1. In a phase 2 clinical study, individuals with AD had better cerebral glucose metabolism and less brain damage (Huang et al. 2020; Salomone et al. 2012).

As a single point, MPC is essential for pyruvate entry into the mitochondrial matrix, which in turn affects the energy metabolism that is impaired in PD. Treatment with MSDC-0160 enhanced motor behavior, reduced dopaminergic denervation, and diminished neuroinflammation and mTOR activity in unilateral 6-OHDA mice. Concurrently, MSDC-0160 treatment significantly altered energy metabolism, as seen by an increase in glutamate oxidation, β-oxidation, and ketogenesis to meet energy requirements and preserve energy homeostasis(Mallet et al. 2022). Its neuroprotective and anti-inflammatory characteristics were validated in a pre-clinical investigation using experimental models of PD (Ghosh et al. 2016).

Targeting Mitochondrial Biogenesis

A growing body of evidence supports beneficial effects of drugs targeting PPARγ-PGC1α-NRF2 in NDD. Pioglitazone, an FDA-approved medication, have been demonstrated to enhance biogenesis and mitochondrial function in diabetes individuals (Scarpulla 2011). Positive outcomes from pre-clinical research point to its potential for use in the treatment of neurological disorders linked to mitochondria

Fig. 4 Possible Pathway in targeting mitochondrial pyruvate carrier to treat NDD. MPC-1, mitochondrial pyruvate carrier; α KG, alpha ketoglutarate; mTOR, mammalian target of rapamycin; ERR-α, estrogen-related receptor alpha; LAP, lapatinib ditosylate. Inhibition of MPC-1 through suppression ERR-α, inhibits mTOR hyperactivity and also shifts the source to glutamate for energy via oxidation which results in reduction of excitotoxicity mediated by glutamate. Inhibition of mTOR directly or indirectly ameliorate the neuroinflammation in NDD
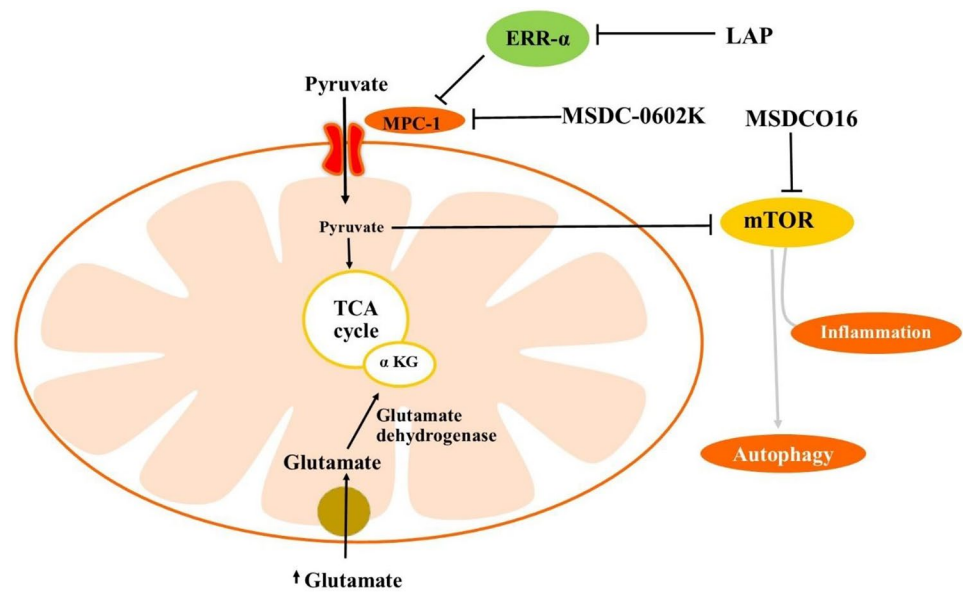
(Masciopinto et al. 2012). A PPAR activator, thiazolidinediones (TZDs) has shown to improve cognitive impairments in AD via stimulating mitochondrial biogenesis (Cheng et al. 2015; Heneka et al. 2015; Risner et al. 2006; Watson et al. 2005). Analogous results were seen with resveratrol and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) through AMPK thereby activating mitochondrial biogenesis (Vingtdeux et al. 2010). Resveratrol also decreases neurodegeneration via activating PGC-1α in AD, PD, HD, and ALS (Blanchet et al. 2008; Ho et al. 2010; Kim et al. 2007; Whitaker et al. 2016). Furthermore, melatonin improved PGC-1α signaling and also restores mitochondrial structure and function in AD (Simmons et al. 2020). In addition, resveratrol increases TFAM expression along with PGC-1α in animal model of PD, demonstrating improved biogenesis (Peng et al. 2016). Treatment with LY344864 improved the expression PGC-1α in different brain regions in PD (Scholpa et al. 2018).

The efficiency of pioglitazone was found in treatment of X-linked adrenoleukodystrophy (X-ALD) which is a neurodegenerative condition marked by mitochondrial and peroxisomal dysfunction, is being studied in a phase 2 clinical trial (Investigators 2015). Rosiglitazone, bezafibrate, and REN001 are additional medications that stimulate the PPAR-PGC-1 axis. Rosiglitazone specifically reduces mitochondrial dysfunction by boosting mitochondrial mass and bezafibrate boosts the ability of mitochondria to produce ATP by boosting mitochondrial proteins. It also found to ameliorate mitochondrial dysfunction in mHtt expressing neurons (Quintanilla et al. 2008). Sirtuin 1 (Sirt1) and AMPK are some potential targets to regulate PGC-1α and reestablish mitochondrial function. For both proteins, a number of activating substances have been discovered, some of which are now undergoing clinical trials for disorders linked to the mitochondria. Sirt1 activity may be controlled pharmacologically via allosteric modulators, also known as Sirt1-activating substances (STACs). Alternately, NAD + precursors often referred to as NAD + boosting molecules (NBMs), targets enzymes that activate NAD + production or prevent its breakdown, can be used to stimulate Sirt1 activation. The use of STACs and NBMs as prospective agents for neurodegenerative disorders associated with mitochondrial malfunction has been suggested by studies using murine models (See Fig. 3). Furthermore, the substantial findings supports the role of SIRT 1 agonists quercetin and resveratrol stimulate the mitochondrial biogenesis by activating sirtuins and AMPK, poses their beneficial effects in NDD (Cerutti et al. 2014; Morató et al. 2015; Valko et al. 2007). Triterpenoids have been shown to promote expression of gene elaborated in mitochondrial biogenesis, thereby activating NrF2 signaling (Tufekci et al. 2011).

Targeting Mitochondrial Dynamics

An important physiological mechanism called mitochondrial dynamics occurs in the appropriate arrangement of positioning of mitochondria in areas with high energy needs by coordinating fission and fusion activities. Neurodegenerative disease development is linked to changes in mitochondrial dynamics. Despite the fact that several genetic, pharmacological, and cellular investigations have suggested that mitochondria play a central role in the development of AD, anomalies in mitochondrial dynamic function are likely to contribute to mitochondrial and neuronal dysfunction (Fig. 4) (Reitz 2012; Smith et al. 1997). Recent research has focused on possible treatments for neurological diseases that target the fission proteins Drp1 and the fusion protein Mfn2.

According to two studies, in both APP and tau transgenic models, the prevention of mitochondrial fragmentation by partial Drp1 impairment is adequate to reduce mitochondrial dysfunction resulting in synaptic loss (Kandimalla et al. 2016; Manczak et al. 2016).

Lysine deacetylases (KDAC) inhibitors have been reported to increase histone H3 acetylation and reduce Fis1 expression levels along with Drp1 recruitment without altering other fusion and fission proteins. These results suggest that mitochondrial elongation has been resulted from downregulation of Fis1 (Lee et al. 2012; Zhao et al. 2011).

Another compound quinazolinone which act as a Mdivi-1 inhibitor, found to selective inhibits DRP1 GTPase activity and thus impart neuroprotection and reduces mitochondrial fragmentation in AD and PD (Bordt et al. 2017; Manczak et al. 2019).

Targeting Mitochondrial Quality Control and Metabolism

The cell manages its mitochondria in an order includes both intra-mitochondrial activities like heme, protein replacement and activities like fusion, fission, mitochondrial biogenesis, and mitophagy. The combination of these mechanisms demonstrates MQC, which is particularly crucial in cellular illnesses ranging from basic mitochondrial hereditary defects to secondary mitochondrial diseases such as neurodegenerative, and inflammatory disorders (Cai and Tammineni 2016; Chang et al. 2020; Chen and Chan 2009). These conditions' genetic and biochemical variability is strikingly comparable to that of several acquired disorders defined by metabolic as well as oxidative stress, exhibiting broad variability. This biologic variation reflects cell-specific and repair mechanisms, complicating reasonable pharmaceutical treatments not only for primary but also secondary mitochondrial diseases. Moreover, novel mitochondrial dynamics and turnover ideas, as well as new mitochondrial illness models, are giving opportunity to create and test MQC-based treatments (Nunnari and Suomalainen 2012; Warda et al. 2013).

Past studies have shown that there is equilibrium among mitochondrial fusion and fission in Alzheimer's disease, which contributes to disorders pathophysiology. Numerous different investigations have discovered that the production of the Fis1 and the DRP1 are elevated in AD individuals and mutant APP-expressing AD animal models. Interruptions in mitochondrial proteostasis were reported repeatedly in AD. The accumulation of Aβ in AD, directly blocks the import channels, causing mitochondrial protein import to be disrupted and pre-protein maturation to be hampered. These disruptions result in mitochondrial malfunction (Goyal and Chaturvedi 2020). In Parkinson's disease,

irregular mitochondrial dynamics have been documented. It has been demonstrated that alpha-synuclein regulates mitochondrial morphology directly. Recent research has shown the molecular pathways causing alpha-synuclein induced mitochondrial morphological defects. The oligomeric alpha-synuclein attaches to the lipids in the OMM, disrupting membrane curvature and slowing mitochondrial fusion (Gilmozzi et al. 2020; Shaw et al. 2005). The number and form of mitochondria may be influenced by fission and fusion events. Quercetin, a flavonoid chemical derived from onions, and the herbal medicine bupleurum. Its therapeutic effects include increased anti-inflammatory and anti-tumor action. Furthermore, Quercetin has a substantial antioxidant impact on several cell types (Khan et al. 2018; Sandhir and Mehrotra 2013). Quercetin and icariin suppress excess mitosis in mitochondria generated by ROS or cAMP-dependent protein kinase and preserve normal mitochondrial number and quality (Kale et al. 2021; Liu et al. 2020; Tiwari et al. 2021). Resveratrol has the ability to drastically control Drp1 production, enhance mitochondrial lengthening, and boost parkin and PINK1 translocation. Resveratrol also considerably increases LC3-II expression at the same time. Additionally, it protects against oxidative stress produced by hypoxia/reoxygenation injury induced oxidative stress and the mitochondrial apoptotic pathway (Li et al. 2019). Another study reported that GTPase inhibitors such as dynasore regulates the expression of Drp1, ameliorating the motor deficits in PD. The study demonstrated that inhibition of Drp1 prevented excessive mitophagy and mitochondrial fragmentation via regulating the expression of PINK1 and parkin, thereby maintain mitochondrial homeostasis in PD (Feng et al. 2021b).

Other Approaches

Genome Editing and Gene Therapy

Modern genome editing tools are opening up new possibilities for gene therapy for a variety of disorders. Any nucleic acid, for gene addition and deletion like siRNA, cDNA, antisense oligonucleotide, RNA, or DNA editing enzyme, microRNA, can be delivered as a genomic carrier using transgenic methods. This method is used for delivery of cDNA delivery for the nerve growth factor (NGF), human aspartoacylase (ASPA), survival motor neuron (SMN), and AADC, and it has been found to be efficient and well tolerated (Hudry and Vandenberghe 2019). Despite of failure in early clinical trials to provide adequate therapeutic benefits gene therapy is rapidly becoming an important treatment approach for a variety of neurodegenerative conditions like AD, PD, and HD, principally suited for well-established and validated genetic models. Various viral (Adeno associated vectors and lentiviral vectors) REF (Marks et al. 2010; Rafii et al. 2018)

and non-viral (Liposomes and nanoparticles) REF (Niu et al. 2017) gene vectors have been studied targeting neurodegenerative disorders. Also being intensively researched and improved delivery methods, such as direct injection or carriers such as liposomes and AAV9. Although, gene therapy using non-viral vectors has not yet been licensed as a treatment for neuronal degeneration, recent developments have created a lot of interest. A plethora of clinical and preclinical studies has been reviewed and describe the current advances of gene therapy for neurodegenerative illness (Chen et al. 2020). Future therapies are focused on editing the genes influencing mitochondrial dynamics. Additionally, overexpression of dynamic and stress controllers gene of mitochondrial, including HSP70, PGC-1, and TFEB, lessens neuronal damage in PD and HD, indicating that the technique may be important approach for various other neurodegenerative disorders (Li et al. 2013; Valdés et al. 2014). An additional cutting-edge method to treat mitochondrial dysfunction is mitochondrial transplantation is proven to be effective in treating neurodegenerative disorders. The delivery of mitochondria has been investigated in many PD models, which restored mitochondrial respiratory function enhanced mitochondrial activity, increased cell viability, and decrease of oxidative stress (Chang et al. 2019).

Caloric Restrictions and Exercise

There are other strategies aimed to enhance mitochondrial function to treat neurodegenerative diseases, it includes caloric restrictions and exercise. The goal of calorie restriction (CR) is to reduce caloric consumption while maintaining adequate nutritional levels and preventing malnutrition. ROS generation is reduced by CR, along with oxidative DNA damage and the aging-related transcriptional alterations. It is believed that sirtuins play a significant part in facilitating the positive role of CR on lifespan. Comparable to CR, overexpression of SIRT1 aids in extending life and lowering illness symptoms associated with neurodegenerative disorders (Cantó and Auwerx 2009; Cunha-Santos et al. 2016). CR stimulates autophagy and suppresses the PI3K/AKT pathway that may enhance atophagy and preserve mitochondria. Furthermore, CR-activate deacetylation of SIRT 3 and inhibition of cyclophilin D, ultimately prevents excitotoxicity. CR increases number of mitochondrial cristae and number of mitochondria (Khraiwesh et al. 2014).

Physical exercise is one of the most promising preventive measures for NDD progression. Exercise increases the biosynthesis, respiration, dynamics, and quality control of mitochondria in skeletal muscle. In neurodegenerative diseases like AD, there are well-established abnormalities in mitochondrial biogenesis and oxidative phosphorylation. Recent reports showed regular, moderate exercise appears to be especially effective at promoting mitochondrial biogenesis

(Burtscher et al. 2021; Upaganlawar et al. 2021). Exercise boosts the ability of the mouse hippocampus to repair damaged DNA by activating mitochondrial uncoupling proteins (UCP) to control proliferation and ROS generated from the mitochondria (Andrews et al. 2005). In a animal model of AD and PD, exercise augmented the activity of multiple mitochondrial respiratory chain complexes (Bo et al. 2014; Schmidt et al. 2021). But the beneficial benefits of exercise on AD and PD patients are predominantly mediated by improved mitochondrial activity is yet to confirm (Frederiksen et al. 2018). The future challenge will be finding and analyzing the best exercise treatments for patients with neurodegenerative disorders. These efforts should provide practical therapy alternatives that patients may use at home.

Future Directions

Scientists anticipate that subsequent treatment efforts will consist of a combination of techniques addressing mitochondrial dysfunction from various sites of entry. It is difficult to determine which of the proposed techniques, and which combination, will be the most useful, if any. A positive perspective is that the discipline has unquestionably entered the therapy age. A plausible scenario is that a therapy for mitochondrial dysfunction will take several years from now. Apparent ideas, such as the link connecting mitochondrial malfunction and elevated and damaging ROS production, are far more nuanced than often assumed. Considering the absence of a treatment, it is critical to diagnose mitochondrial diseases since they are a common source of inherent metabolic inefficiencies. As a result, it is critical to raise mitochondrial information among researchers in order to discover novel mitochondrial targeted treatment. As there is the lack of treatment, the diagnosis of a mitochondrial disorder is critical for preventing further mitochondrial malfunction. To ensure safety in translation to humans, it is necessary to have a deeper knowledge of the molecular mechanisms. This includes developing biomarkers that can detect mitochondrial activity and the ability to trigger a healthy stress response. This article will provide a review of several promising developments as well as the numerous hurdles that remain in the search of the successful therapy for mitochondrial disorder.

Conclusion

Significant progress has been achieved in the development of therapeutic approaches in order to restore mitochondrial homeostasis. Mitochondria represent a crucial therapeutic target for a number of prevalent debilitating illnesses. However, there are still a lot of difficulties in developing

new drugs for mitochondrial medicine. Additionally, there are a staggering number of pharmaceuticals, both synthetic and natural extracts that target this organelle. However, further development is required to provide novel treatment approaches, such as gene therapy techniques.

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Declarations

Ethics Approval Not applicable.

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