Life Sciences 218 (2019) 165–184

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Crosstalk between mitochondrial dysfunction, oxidative stress, and age related neurodegenerative disease: Etiologies and therapeutic strategies

Hasnaa A. Elfawy, Biswadeep Das*

School of Biotechnology, KIIT deemed to be University, Campus XI, Bhubaneswar 751024, Odisha, India

ARTICLE INFO

Keywords:
Mitochondrial dysfunction
Oxidative stress
Neurodegenerative disease
Mitochondrial heteroplasmy
Therapeutic strategies

ABSTRACT

Mitochondrial function is vital for normal cellular processes. Mitochondrial damage and oxidative stress have been greatly implicated in the progression of aging, along with the pathogenesis of age-related neurodegenerative diseases (NDs), such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Although antioxidant therapy has been proposed for the prevention and treatment of age-related NDs, unraveling the molecular mechanisms of mitochondrial dysfunction can lead to significant progress in the development of effective treatments against such diseases. Aging is associated with the generation and accumulation of reactive oxygen species (ROS) that are the major contributors to oxidative stress. Oxidative stress is caused because of the imbalance between the production of ROS and their oxidation, which can affect the mitochondrial respiratory chain function, thereby altering the membrane permeability and calcium homeostasis, along with increasing the heteroplasmic mtDNA and weakening the mitochondrial defense systems. Mitochondrial dysfunction mainly affects mitochondrial biogenesis and dynamics that are prominent in several age-related NDs. Mitochondrial dysfunction has a crucial role in the pathophysiology of age-related NDs. Several mitochondria targeted strategies, such as enhancing the antioxidant bioavailability via novel delivery systems, identifying unique mitochondrial proteins as specific drug targets, investigating the signaling pathways of mitochondrial biogenesis and dynamics, and identifying effective natural products are potentially effective to counteract mitochondrial dysfunction-related NDs.

1. Introduction

Mitochondria are the chief sources of energy production in eukaryotic cells, and play a critical role in cell growth, differentiation, cellular signaling, apoptosis, and cell cycle control. Mitochondria are bounded by two effectively distinct membranes; an outer and an inner membrane that is folded into cristae and comprise about 100 proteins clustered within specific 'complexes' on the inner membrane; the interplay between these complexes generates adenosine triphosphate (ATP), the universal energy currency of all cells. Most mitochondrial proteins are transported from the cytoplasm to mitochondria through particular protein translocator complexes [1]. The connections between these complexes assist in bringing the outer and inner membranes of mitochondria close together [2]. The interplay between the outer membrane proteins (OMP) such as hexokinase, voltage-dependent anion channel (VDAC1), and inner membrane proteins (IMP) such as adenine nucleotide translocator (ANT) link the outer and inner mitochondrial membranes together, combining cytosolic glycolysis with mitochondrial oxidative phosphorylation, thereby facilitating cellular energy metabolism by maintaining a proper ATP/ADP proportion [3] (Fig. 1).

Previously, mitochondria were known to be rigid and isolated structures; however, now they are considered to be highly dynamic structures integrated with many cellular functions. They form a reticular and highly coordinated structure under certain cellular conditions. Furthermore, mitochondria move within the cell in the punctate state or as a reticular unit for providing the foci of energy production, such as at the nucleus during cell division, or to synapses in neuronal cells at times of urgent information transfer. This movement occurs along the microtubules in one direction and along the actin filaments in the other. The transitioning of mitochondria between punctate and reticulum states through alternating fission and fusion is now known to be critical in maintaining the mitochondrial quality control [4,5]. Mitochondria have the ability to migrate, fuse and divide, and undergo regulated turnover. Recruitment of mitochondria to the critical compartments of the cell depends on the metabolic requirements of the cell. In the cells, mitochondria are distributed near the sites where ATP and other mitochondrial metabolites are in high demand. For example, in

* Corresponding author at: Biswadeep Das, KIIT University, School of Biotechnology, Campus XI, Bhubaneswar 751024, India.
E-mail address: biswadeep.das@kiitbiotech.ac.in (B. Das).

https://doi.org/10.1016/j.lfs.2018.12.029
Received 22 October 2018; Received in revised form 10 December 2018; Accepted 15 December 2018
Available online 20 December 2018
0024-3205/ © 2018 Elsevier Inc. All rights reserved.

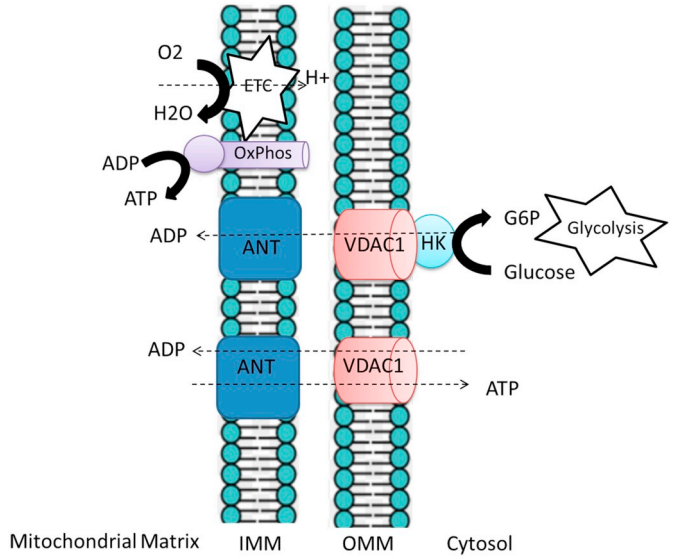

Fig. 1. The interaction between hexokinase-VDAC1-ANT networks and combining glycolysis with oxidative phosphorylation for maintaining a proper ATP/ADP proportion. ETC: electron transport chain; OxPhos: oxidative phosphorylation; ANT: adenine nucleotide translocase; VDAC1: voltage dependent anion channel; HK: hexokinase.

neurons, a specialized area known as the “axon hillock” exists, which is enriched in channels and transporters that require ATP. Hence, there are also an increased number of mitochondria in the axon hillock [6]. One of the important fitness features of mitochondria is their ability to move in defined ways along with microtubules. Remodeling of the microtubule structure plays a crucial role for the cell to respond to metabolic stress [7]. Relying on these metabolic changes, mitochondria can be redistributed in the cell via this dynamic network. As a consequence, mitochondria promptly adapt to any physiological or environmental change in the cells [8].

Over 1000 proteins, most of which are encoded by the nuclear genome are present in the mitochondria. Mitochondria are quasi-independent from the rest of the cell; they have their own DNA (mtDNA) and encode 13 essential proteins that are translated on the mitochondrial ribosomes prior to assembly, which play vital roles in the regulation of cellular bioenergetics. Human mtDNA is circular in shape and 16,569 bp in length [9]. It consists of approximately 1500 genes, 37 encoded by the maternally inherited mtDNA and the remainder encoded by the nuclear chromosomes. Inherited mtDNA mutations have been responsible for the etiology of several human diseases [10]. Mitochondria can synthesis their own lipids, which is an essential process for the division of mitochondria without depending on the smooth endoplasmic reticulum (ER) [11].

Proton motive force is the action that uses the proton gradient to drive the synthesis of ATP. Similar to man-made power plants that produce electrical energy by using the flow of wind, water, or steam to rotate a turbine, synthase synthesizes ATP by using the proton motive force from one side of the inner membrane to the other to rotate protein subunits. If there is no proton gradient, synthase subunits stop rotating, and the cell can quickly become starved of energy and die. Therefore, the protein complexes and small molecules that establish and maintain this gradient play an essential role in the life of the cell [12]. There are four protein complexes numbered I through IV in this system. Complexes I, III, and IV directly pump protons from the matrix into the intermembrane space. Complex II does not directly pump protons; however, it promotes proton pumping in complexes III and IV. Proton pumping requires energy, and the four protein complexes get energy by transferring electrons through a series of coupled reactions. This linked process of electron transport is the reason for which the four complexes are collectively referred to as the electron transport chain (ETC) (Fig. 2). In the absence of oxygen, the electron transfer comes to a halt, meaning that ATP synthesis also halts. Indeed, the reason we breathe oxygen is such that it can serve as the final electron acceptor at the end of the ETC. Collectively, complexes I, III, and IV function as proton pumps during ATP production, and complex II directly connects Krebs cycle with the mitochondrial ETC, oxidizing succinate to fumarate in Krebs cycle and reducing ubiquinone in the ETC [13]. Despite complex II being less significant for free radical formation, a recent study suggests it can generate large amounts of reactive oxygen species (ROS) under low succinate conditions, when complexes I and III are inhibited [14]. A schematic representation of mitochondrial metabolism and dynamics is depicted in Fig. 3, which shows the membranes, intramembranous space, and the matrix of mitochondria that coordinate energy production and the concomitant generation of oxidative species, fusion and fission cycles, and apoptosis.

Mitochondrial dysfunction is associated with several developmental and age-related diseases, predominantly neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [15,16]. Neurodegeneration leads to the loss of normal anatomy and function of the neuronal system in the human body. Abnormal folding and accumulation of proteins within the neuronal cell bodies are the hallmarks of most neurodegenerative diseases. Such changes in the normal protein metabolism often cause neuronal cell death and dysfunction of the affected regions of the central nervous system [17,18]. The role of mitochondrial dysfunction in the progression of neurodegeneration is intriguing. MtDNA executes several metabolic processes in the human body, like Krebs cycle and ETC to generate energy. Often, the circular mtDNA accumulates several mutations as a person ages. Such mutations might lead to mitochondrial dysfunction, which can initiate several complications in the human body, including the initiation and progression of neurodegenerative diseases [19–23]. The exact reason for mitochondrial dysfunction is unclear; however, it is documented that mtDNA mutation, oxidative damage, and/or aggregation of mitochondrial proteins leading to abnormal mitochondrial morphology are the main reasons for mitochondrial dysfunction. Among these, oxidative stress is one of the critical factors, responsible for mitochondrial dysfunction, because oxidative stress can damage mitochondrial proteins, nucleic acids, and lipids, and can further assist in the generation of intracellular ROS, which can lead to mtDNA mutations [15].

ROS are molecules with an unpaired electron, including peroxides, superoxide, hydroxyl radical, and singlet oxygen, and are hence very reactive and toxic to the cells. ROS are “redox reactive” and affect different cellular components in multiple ways. For example, ROS can oxidize proteins and can negatively affect the active sites of the enzymes, thereby inhibiting proper binding of the substrate. ROS are extremely damaging to the susceptible neurons, because they require high energy, and have large numbers of mitochondria, high presence of fatty acids, reduced capability of limiting glucose uptake, weak antioxidant defense, and weak bioavailability to antioxidant treatment and molecules. ROS are also known to accelerate aging and cause damage to many cells in the body, including neurons [24].

2. Mitochondrial biogenesis

For mitochondrial biogenesis, proteins and lipids are required to be imported and synthesized in the mitochondria. Mitochondria have the ability to synthesize several lipids, such as phosphatidylethanolamine, phosphatidylglycerol, and cardiolipin (CL), whereas other lipids must be transported. Lipid synthesis occurs mainly in the ER, whose membrane is connected with the outer mitochondrial membrane at sites, called the mitochondria-associated membrane (MAM). Vesicular traffic and lipid transfer proteins also participate in lipid transport to the mitochondria. Mitochondrial-targeted precursor proteins pass through

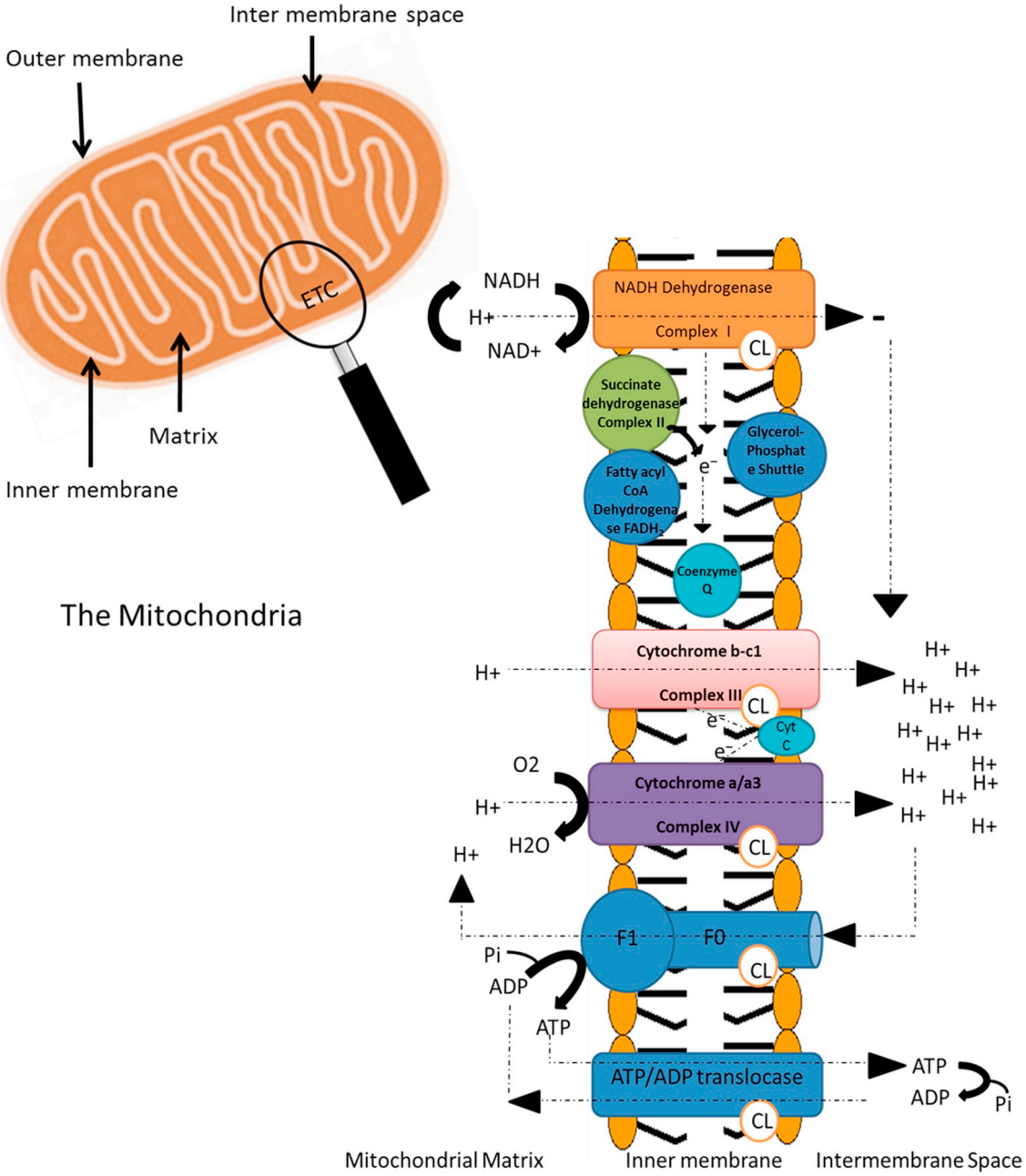

Fig. 2. Magnification of the inner membrane of the mitochondria and generation of ATP in the oxidative phosphorylation, as well as the interaction of CL with oxidative phosphorylation complexes. The electrons are moved along the path shown in the figure, resulting in the reduction of oxygen to water at complex IV. During this process, protons (H+) are pumped by complexes I, III and IV into the intermembrane space to form an electrochemical gradient, which is utilized by F0F1-ATPase to synthesize ATP from ADP and inorganic phosphate (Pi). ATP formed is then transferred by the ADP/ATP translocase to the intermembrane space in exchange with ADP. NAD^+: Oxidized form of Nicotinamide Adenine Dinucleotide; NADH: Reduced form of Nicotinamide Adenine Dinucleotide; CL: Cardiolipin; F0-F1: Oxysomes for ATP synthesis; ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; Cyto c: Cytochrome *c*.

the membranes via “translocase of the outer membrane” (TOM), and then, segregate into two fundamentally unique “translocases of the inner membrane” (TIM): TIM23 and TIM22 [25]. Transport of massive proteins requires unfolding during shuttling and refolding to native conformers to recover function. Most of the mitochondrial proteins are synthesized on the cytosolic ribosomes, and imported through the TOM channel complex, and then sorted by different sorting types of machinery [26] (Fig. 4).

Due to the lack of a variable number of transfer RNA (tRNA) genes in mtDNA, mitochondria import tRNAs. VDAC is a key regulator; hence, TOM and TIM23 are additionally involved in this process [27]. ATP hydrolysis is used to facilitate tRNA import. Translocation of tRNA occurs via two broad mechanisms: first, tRNA is transported from the cytosol to mitochondria through the protein import pathway; and the second mechanism occurs mainly in plants and protozoans and is not understood clearly. tRNAs are directly imported independently of cytosolic soluble factors. Under in vitro conditions, both yeast and human tRNA Lys have been found to be transported into human mitochondria under specific circumstances, thereby proposing a potential way to deal with treating some mitochondriopathies related to dysfunctional mitochondrial tRNA mutations [28].

Mitochondrial biogenesis is regulated by numerous signaling pathways in response to various stimuli, and is a complicated process requiring synthesis, import, and incorporation of proteins and lipids to

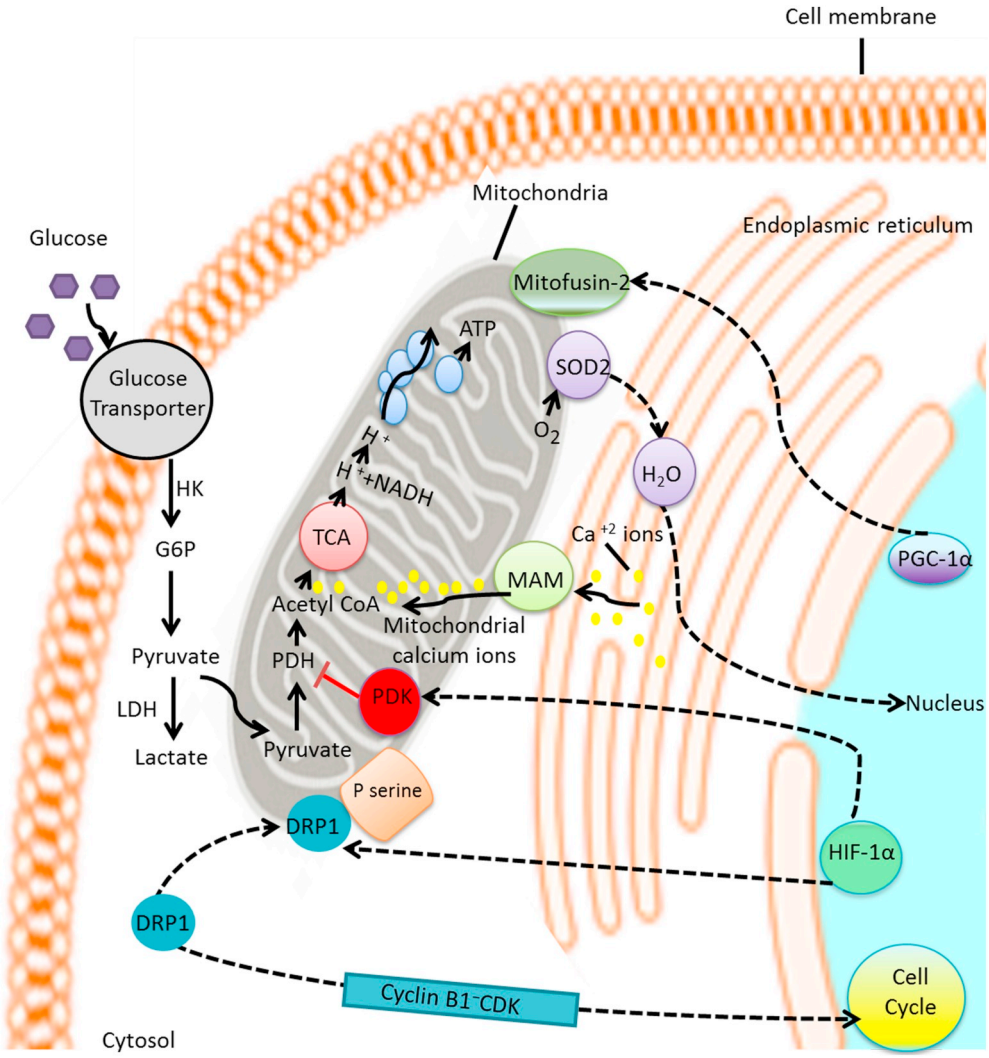

Fig. 3. Mitochondrial Metabolism and Dynamics. The membranes, intramembrane space, and the matrix of mitochondria coordinate the ATP production, generation of oxidative species, fusion, fission, and apoptosis. Pyruvate dehydrogenase (PDH), the major regulator of oxidative metabolism, is inhibited through pyruvate dehydrogenase kinase (PDK) or activated by increased mitochondrial calcium. Glucose is transported to the cytoplasm of the cell through specific transporter and it's converted to pyruvate which is the end product of the glycolysis. Conversion of pyruvate to acetyl coenzyme A (CoA) occurs in the mitochondria or, if mitochondrial metabolism is inhibited, is converted to lactate by lactate dehydrogenase (LDH). Mitochondrial pyruvate is metabolized to feed the Tricarboxylic acid cycle (TCA), which contributes electron donors NADH to pass electrons down the ETC comprised of four megacomplexes found in the cristae. This results in the accumulation of H^+ ions in the intermembrane space, driving the synthesis of ATP from ADP and inorganic phosphate as controlled by ATP-synthase. The electron flux also generates reactive oxygen species (ROS), such as the superoxide anion (O_2^-), which are converted to the diffusible redox signaling molecule hydrogen peroxide (H_2O_2) by superoxide dismutase 2 (SOD2). Mitofusin protein that regulates fusion is found in the outer membrane. The fission mediator Dynamin-Related Protein 1 (DRP1) is typically cytosolic, but upon phosphorylation of serine 616, translocates to the outer membrane. Mitochondrial fission and nuclear division are organized via a link between DRP1 and the cyclin B1-cyclin-dependent kinase (CDK). Peroxisome-proliferator-activated receptor - coactivator 1(PGC-1) and hypoxia-inducible factor 1(HIF-1) also regulate transcriptional control of fission and fusion. Calcium, which can move from the endoplasmic reticulum ER to the mitochondria via mitochondria-associated ER membranes (MAMs), regulates PDH activity and apoptosis. The relation between mitochondria and the ER also create microenvironments that direct fission.

the existing mitochondrial reticulum as well as mtDNA replication. Peroxisome proliferator-activated receptor–gamma coactivator 1 alpha (PGC-1α) is the master regulator of mitochondrial biogenesis and function; it co-activates many transcription factors, including those encoding peroxisome proliferator-activated receptors (PPARs), nuclear respiratory factor (NRF-1 and -2), estrogen-related receptor-α, myocyte enhancer factor-2, forkhead box protein O 1, and sterol regulatory element-binding proteins 48,49, and so, becoming a crucial metabolic node [29,30]. PGC-1α co-activation of NRF-1 and -2 promotes the expression of nuclear-encoded mitochondrial proteins and mitochondrial transcription factor A (TFAM), which is a mtDNA-binding protein and plays an essential role in genome maintenance. Upregulated TFAM transcription is directly associated with increased mtDNA replication and transcription [31,32]. PGC-1α activation is associated with increased energy spending and uptake of energy substrates [29].

Activation of AMP-activated protein kinase (AMPK) plays an important role in regulating mitochondrial biogenesis, namely mitochondria growth and division. Factors activating AMPK, such as oxidative stress, exercise, and caloric restriction affect mitochondrial biogenesis. Accordingly, mitochondrial biogenesis is absent in the mice (dominant-negative) mutant of AMPK 55. AMPK-mediated mitochondrial gene expression involves the activation of PGC- 1α and PPARs [33,34].

3. Mitochondrial dynamics and quality control: fission, fusion, and mitophagy

In the human body, mitochondrial membrane potential of 150 mV across the 5-nm membrane produces an electric field strength of 30 million volts per meter, which is equal to the energy discharged by a bolt of lightning in the sky. This electric energy supported the evolution process of several structures in more diverse combinations over time [35]. The origin of mitochondria over generations depends on the evolutionary process called endosymbiosis or “mutually-beneficial relationship”. The integration of tiny bacteria into the host Archaea ultimately led to the exchange of DNA, which became co-dependent on each other in order to live as one organism [36]. The fitness of mitochondria is the fundamental feature and the compartmentalization is very crucial for its dependency. Mitochondrial chromosome actively control their behavior; and so, it is highly dynamic and undergoes fission and fusion and programmed degradation (mitophagy) (Fig. 5). Biogenesis of mitochondria is regulated by PGC-1α, which activates NRF-1 and NRF-2, and TFAM and transcription factor B mitochondrial (*TFBM*) [31,32]. Cycles of fusion [controlled by mitofusin (MFN) 1, MFN2, and optic atrophy protein 1 (OPA1)] [37] and fission [controlled by dynamin-related protein-1 (Drp1) and fission 1 (FIS1) form elongated mitochondrial networks and smaller individual organelles,

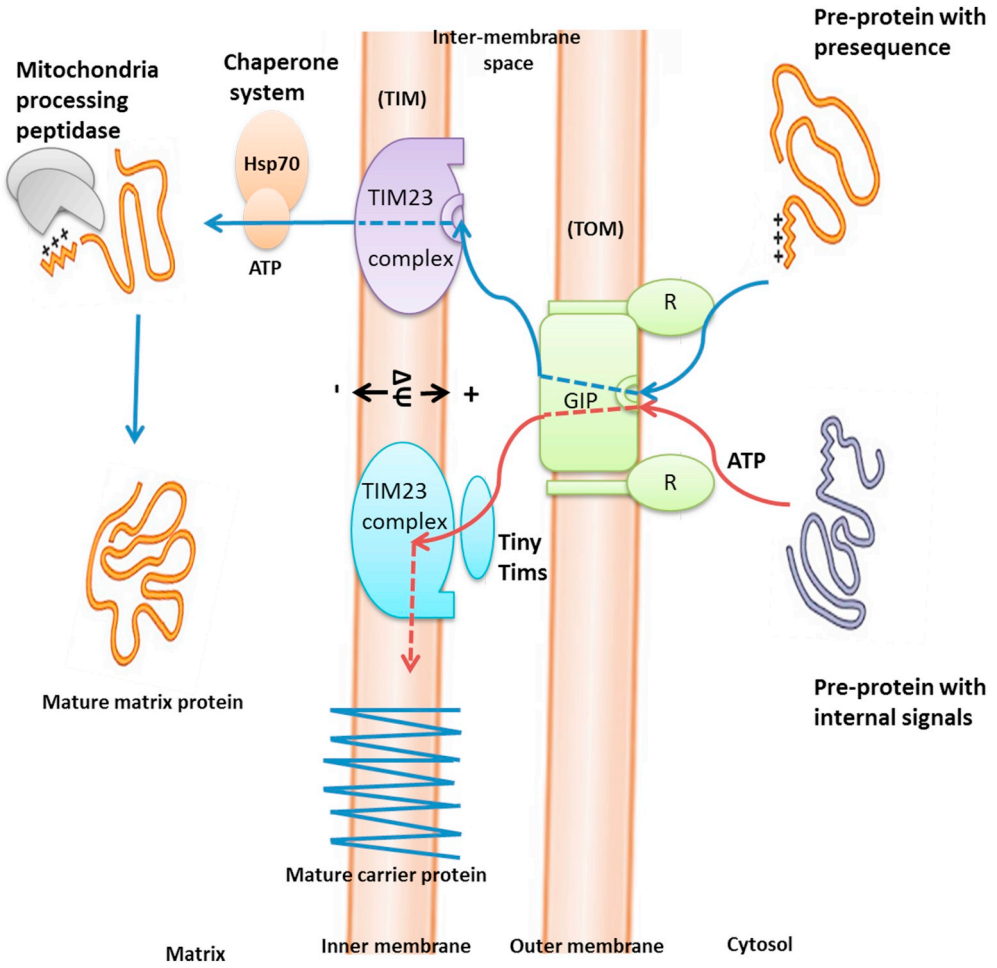

Fig. 4. The mitochondrial protein import machinery from the cytosol to the matrix. The translocase of the outer mitochondrial membrane (TOM) has receptors and a general import pore (GIP) to import most of the mitochondrial proteins. Proteins with presequences (orange) are transported to the matrix by the translocase of the inner membrane (TIM23) complex. This requires the membrane potential ($\Delta\psi$) and the ATP-dependent action of mitochondrial heat-shock protein 70 (mtHsp70). The mitochondrial processing peptidase (MMP) removes the presequence. Preproteins with internal signals (gray) are guided by tiny Tim proteins across the intermembrane space to the TIM22 complex of the inner membrane and inserted into lipid phase of the inner membrane in a $\Delta\psi$-dependent step. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

respectively. Fission provides a mechanism to isolate the damaged components during a normal lifespan or during increased oxidative stress for elimination [38,39]. Mitophagy involves mitochondrial depolarization and a series of protein-regulated steps that ultimately culminates in fusion with the lysosome P62, and also plays a role in targeting cargo to the autophagosome, which is subsequently degraded during active autophagy. Assembly of the phagosome involves beclin-1 and conjugation of microtubule-associated protein 1 light chain 3 (LC3) onto phosphatidylethanolamine to form LC3-II [40]. They also possess the ability to traverse at varying speeds within the cells, which is particularly crucial for the neurons with long cell processes [4].

Mitochondrial fusion occurs when the double membranes of two neighboring mitochondria fuse. During this process, fusion controls mitochondrial morphology, maintains mitochondrial functions, including oxidative phosphorylation, membrane potential, and DNA replication/repair, by allowing the exchange of DNA, proteins, and metabolites. GTPases regulate fusion and fission; Drp1 drives fission, and the collaboration of Mfn1 and Mfn2 on the outer membrane along with dynamin-related protein, Opa1 and Opa3 facilitates fusion with the inner membrane [41,42].

Mutations in OPA1 and MFN 2 cause two neurodegenerative diseases: dominant optic atrophy (DOA) and Charcot Marie-Tooth type 2A, respectively [43,44]. Degeneration of neurons is also prominent in mice with a targeted mutation in MFN 2 [45]. Lack of mitochondrial fusion leads to a severe defect in the respiratory capacity. The fragmented mitochondria are a result of the imbalance in mitochondrial dynamics (fusion < fission); it becomes functionally different, assembling heterogeneity in the membrane potential and mtDNA nucleoids, which encode ETC components. These findings highlight the protective role of mitochondrial fusion against the implications of its fission [46].

Fusion induces mixing of mitochondrial contents, including the mixing of mitochondrial genomes, thereby allowing the dilution of damaged mtDNA or other damaging factors to buffer/mitigate against stresses. Mitochondrial fission plays a critical role in segregating the dysfunctional mitochondria. During this process, an impaired daughter organelle can be recovered by fusing with healthy mitochondria or eliminated by autophagy [47]. Mitochondrial Fis1 and Drp1 control and regulate fission. Upon activation, Drp1 moves from the cytosol to the outer mitochondrial membrane, binds to adaptor proteins, and constricts the outer and inner membranes [48]. Impairment of mitochondrial fission due to a missense mutation in the dynamin-1-like gene leads to progressive energy deficiency. Drp1 dominant mutations have been linked to a lethal neurodegenerative condition manifesting multiple phenotypes, including microcephaly, optic atrophy, and lactic acidemia. Extensive studies on mouse models suggest that there are multiple tractable models for studying the implications of these mutations [49].

In addition, using knock-out mice, two groups independently found that loss of Drp1 resulted in embryonic lethality [50]. Similar results were reported for the “Python” mouse, in which a middle domain mutation in *Drp1* produced embryonic lethality. Specific defects in placental cell development were observed in *Drp1*$-/-$ embryos, including a missing trophoblast giant cell layer [51].

With regards to fission, limited number of compounds are present that specifically regulate mitochondrial fission and fusion, such as mitochondrial division inhibitor (Mdivi-1) that inhibits Drp1 and 15-

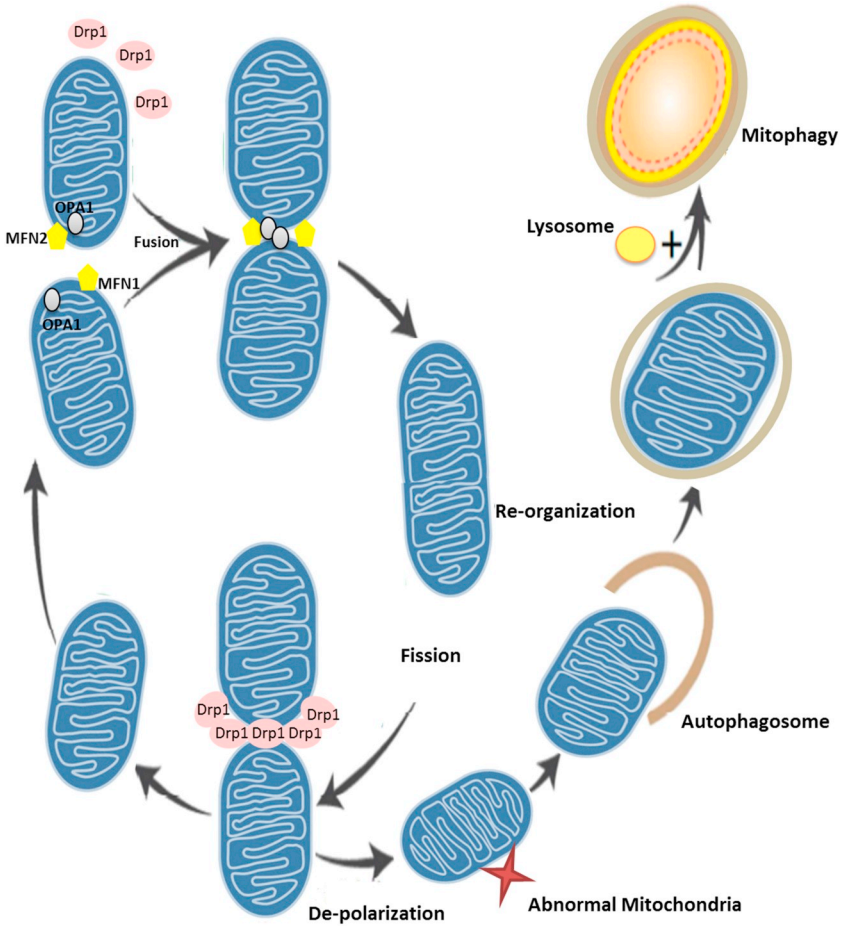

Fig. 5. The mitochondrial life cycle and how mitochondrial dynamics and mitophagy contribute to quality control. Mitofusin (MFN) 1 and 2 are regulated of outer membrane fusion. Optic atrophy 1 (Opa1) is required for mitochondrial inner membrane fusion. Mitochondrial fission is regulated by dynamin-related protein 1 (Drp1). When a daughter mitochondrion is dysfunctional/depolarized, it will be targeted for elimination by recruitment of autophagosomes, which are degraded after fusion with a lysosome.

oxospiramilactone (S3), which in turn inhibit ubiquitin specific peptidase 30 (USP30), a mitochondrial localized deubiquitinase [52]. These molecules can be considered as potential drug targets owing to their pro-fusion attributes; either they block fission (mdivi-1) or enhance fusion (M1, S3).

Mitophagy, a form of quality control for healthy mitochondria, is defined as the process of destruction of dysfunctional mitochondria to maintain the cellular functions by the autophagic machinery, which can occur during the production of mature erythrocytes, or paternal mitochondria degradation or ischemia- and drug-induced tissue injury, neurodegenerative disease or in many different cell types due to the loss of function or damage to the mitochondria. Autophagy is a catabolic degradation process transporting cytoplasmic components to the lysosome, and includes: macro-autophagy, wherein proteins are recruited to the autophagosomes that fuse with the lysosome to degrade the sequestered mitochondria, and micro-autophagy, wherein mitochondrial components are directly incorporated into the lysosomes through membrane invagination. Parkin plays a crucial role in these autophagic mechanisms [53].

Mutations in PARK2 (Parkin) and PARK6 (PINK1) genes, key regulators of mitophagy, induce the onset of juvenile autosomal recessive PD. Briefly, PINK1 protein accumulates on the surface of damaged mitochondria (with reduced membrane potential), binds Parkin, and the E3 ubiquitin ligase activity of Parkin ubiquitinates multiple mitochondrial outer membrane proteins [54]. These ubiquitinated proteins are recognized by specific receptors of the preautophagosome, causing engulfment of the whole mitochondria for the eventual destruction in the lysosome. Mitophagy is closely linked to fusion because mitofusin is regulated by PINK1, which acts as a receptor for Parkin, and is ubiquitinated by Parkin to inactivate it. In addition, PINK1 and Parkin have also been shown to regulate mitochondrial fission and fusion [55]. Several researchers have postulated the hypothesis that in case of PD, the weakest functioning mitochondria that are normally excreted from the cellular pool through mitophagy, are not being excreted owing to the omission of mitophagy, because of mutations in the PINK1 and Parkin genes. This causes the accumulation of damaged mitochondria, which ultimately leads to neuronal death in the *substantia nigra* (SN) [56]. For instance, loss of the mitochondrial membrane protein Uth1p in yeast caused a selective defect in mitophagy and decreased the lifespan of the organism. Mitophagy may help decrease the production of ROS by removing dysfunctional mitochondria [57].

4. Mitochondrial heteroplasmy and threshold effect

Several copies of mtDNA are located in every human cell; on the other hand, there are only two copies of nDNA. The mtDNA of a mammalian cell is the only extra-chromosomal DNA of the cell and is under the dual genetic control of both nuclear and mitochondrial genome. Any dysfunction in the mtDNA may be because of point mutations in the nuclear encoded-genes for various compartments of the ETC or in mitochondrial tRNA or rRNA genes affecting protein expression and rearrangements of mtDNA. The vast majority of mitochondrial proteins are encoded by the nDNA. Mutations in both mitochondrial and non-mitochondrial nuclear genes can affect the function of mitochondria, for example, mutations in the nuclear genes involved in fusion and fission can cause alterations in mitochondrial biogenesis and maintenance [58,59]. MtDNA is specifically susceptible to mutations, which can be maternally inherited or occur sporadically during embryogenesis. Somatic mtDNA mutations occur in old age, and are most likely because of ROS formation. However, as most mitochondrial proteins involved in mitochondrial metabolism and the products involved in mtDNA maintenance (replication and integrity)

are encoded by nDNA, few nuclear-encoded gene mutations are associated with mitochondriopathies [60]. The mode of mtDNA inheritance is exclusively maternal; in contrast, inheritance of nDNA follows a Mendelian pattern for autosomes and the X chromosome; paternal inheritance for the Y chromosome [58]. Homoplasmy is a state of normal cells when all copies of mtDNA are identical or when some mutations affect all copies of the mitochondrial genome (homoplasmic mutation). Heteroplasmy is defined as the occurrence of a mixture of two or more mitochondrial genotypes in the cell (healthy and mutated) (Fig. 6) Replication of mtDNA takes place independently of cell division, and several templates of mtDNA may replicate several times in a cell cycle. At the time during cell division, mitochondria partition between the cells, which may not be always haphazard, and the proportion of abnormal mtDNA can change in different cells. During embryogenesis, cells proliferate and divide extensively, followed by the segregation of replication. Such segregation leads to variations in the distribution of mutant mtDNA among cell lineages, generating homoplasmic and heteroplasmic cell populations with a variable content of mutant mtDNA [56,57]. In heteroplasmy, there is a threshold level of the mutated mtDNA, which is significant for both the clinical manifestations of a disease and biochemical dysfunctions. Relying on the ratio of abnormal mtDNA and the energy requirements for a particular tissue and after a certain phenotypic threshold, functional abnormalities may manifest. This clinical phenotypic threshold rely not only on the proportion between mutant and normal mtDNA, but also on the ability of the cells and tissues to compensate for dysfunctions at the translational, transcriptional, enzymatic, and respiratory levels [61]. Furthermore, the threshold varies among tissues based on different energy needs; the brain is the most sensitive organ to mitochondrial defects followed by the heart, skeletal muscle, endocrine system, kidney, and liver. Depending on the severity of the defect, the functional cell mass within a specific organ may decrease. Some mitochondrial diseases were detected in animal [62] and human models [63] characterized by metabolic syndrome; for instance, lower mitochondrial mass, altered morphology, reduced fatty acid oxidation, accumulation of ROS, and reduced mitochondrial oxidative phosphorylation. Several diseases are caused by mitochondrial dysfunction, such as neonatal fatalities, cancer, type II diabetes, and neurodegenerative diseases [61].

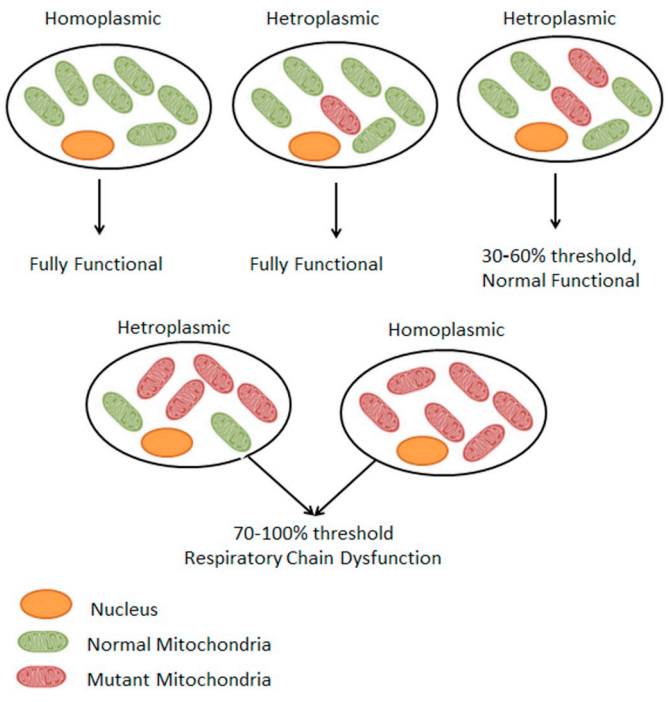

Fig. 6. The heteroplasmic and homoplasmic mitochondria. The nucleus is represented in an orange circle, healthy mitochondrion is represented in green color, and mutated one is represented in red color. Note the difference in the four cases of heteroplasmy is different percentages of the mutant in their mitochondria. The threshold of a mtDNA mutation is related to the degree of heteroplasmy. High percentage of mutation in mtDNA leads to the dysfunctional respiratory chain. Low levels of heteroplasmy in any cell or more generally in a subject give functional respiratory chain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

5. Mitochondria as hotspots of oxidative stress

In the normal cells, mitochondria continuously function for metabolizing oxygen. Electron flow through ETC is a defective process, wherein 0.4–4% of oxygen used by the mitochondria is partially reduced, leading to the generation of "primary" ROS, such as the superoxide anion. Excessive formation of superoxide anion leads to the generation of "secondary" ROS such as hydroxyl radicals [64], which are highly reactive, and can attack DNA and damage purines and pyrimidines, deoxyribose backbone, and can induce mutation. Oxidative stress occurs due to an imbalance in the generation and detoxification of ROS leading to oxidation and damage to proteins, DNA, and lipids. At low concentrations, ROS act as redox signaling molecules, which transduce signals from the mitochondrial compartment to other compartments of the cell. Increased formation of ROS within the mitochondria might induce an adaptive reaction, leading to increased stress resistance and a long-term reduction of oxidative stress. Such kind of reverse effect of the response to ROS stress is known as mitochondrial hormesis or mitohormesis, and is hypothesized to be responsible for the increase in the respective lifespan and health capabilities during glucose restriction and physical exercise [65]. ROS at low concentrations are important for the activation of various genes related to cellular stress response, such as superoxide dismutase (which reduces O_2^- to H_2O_2), catalase, and glutathione peroxidase (which reduces H_2O_2 to H_2O). In prokaryotes, it leads to the activation of SoxR, which mediates *SoxS* gene transcription, resulting in an expression of SoxS protein, thereby inducing the transcription of several other genes, including superoxide dismutase (SOD) The OxyR protein of bacteria acts as a transcriptional regulator of H_2O_2-inducible genes, and has been proved to be directly activated by oxidation [66]. ROS are biologically significant in a variety of physiological systems, including adaptation to hypoxia, immunity, repair processes, differentiation, and longevity. ROS also trigger autophagy/mitophagy process, with consequent removal of damaged mitochondria and in turn enhances cellular survival [67]. Normally, a small amount of ROS is beneficial to the brain, which is involved in cell signaling. However, upon accumulation of ROS because of oxidative stress, proteins and toxic wastes can be deposited in the brain, thereby hampering the function of the brain. Because the brain requires high energy to function, it is very active and does not have the capacity to regenerate unlike other body parts; it is therefore, very susceptible to injury because of oxidative stress [68–69]. Coupled with increased ROS production, decreased production of antioxidant agents such as the antioxidant enzymes can further aid in cell destruction and neurodegeneration [69] in the brains of organisms [70]. ROS are generally produced in the mitochondria during oxidative phosphorylation and can accumulate and damage mtDNA by inducing mutations. The mutated mtDNA can cause more dysfunction of oxidative phosphorylation and mitochondrial morphology, leading to several complications. Once this cycle starts, it does not stop, and is known as the vicious cycle of the mitochondria (Fig. 7), which also impairs the defensive antioxidant system and gradually progresses neurodegeneration. Mitochondrial damage will ultimately bring about the depletion of ATP, influx in calcium, and the opening of the mitochondrial permeability pore, eventually leading to apoptosis. Another mechanism of protein accumulation in the cells is through the destruction of chaperone and proteasomal processes, which are evolved to regulate

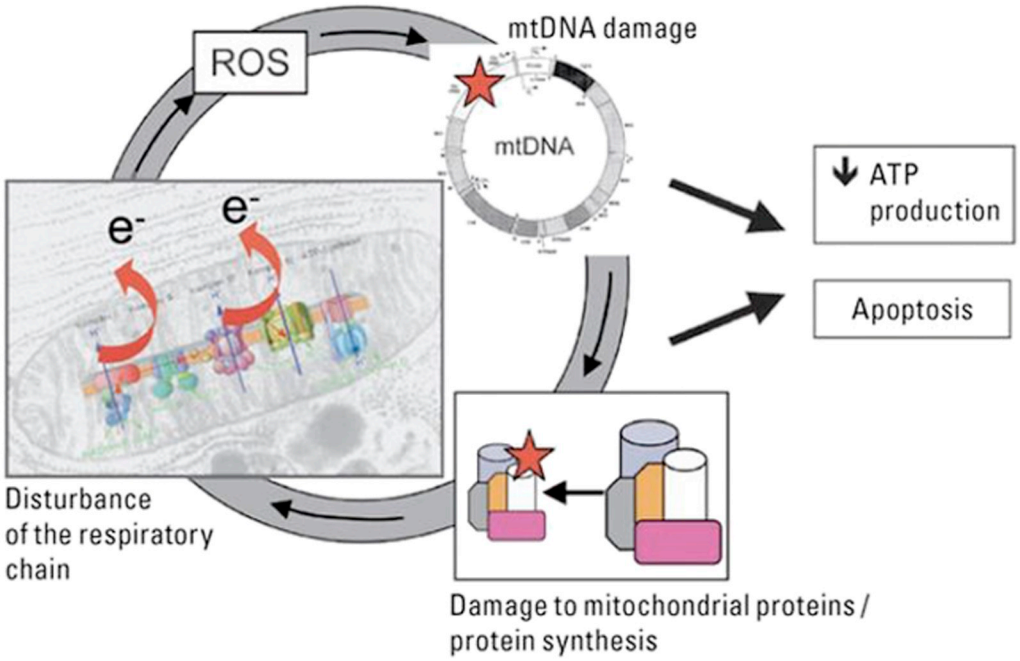

Fig. 7. Depicts the vicious cycle of the mitochondria and its effects on the cell. Reactive oxygen species production, mitochondrial DNA damage, mitochondrial DNA mutagenesis and mitochondrial proteins damage lead to depletion of ATP as well as induction of apoptosis.

protein turnover. ROS regulates the expression of heat-shock proteins, which are highly conserved and facilitate correct protein folding [71]. Therefore, the timely removal of oxidatively damaged proteins is important to maintain normal cellular homeostasis and viability. Although there is evidence suggesting that chaperone mediated autophagy is activated during oxidative stress response [72], the proteasome represents the major proteolytic machinery for the removal of oxidized and misfolded proteins normal proteasome-dependent degradation is essential for cells to cope with oxidative stress [73]. Chaperones function in different ways by co-operating with many different proteins, binding to different substrates and performing changes in the structure of proteins to achieve correct folding. *Heat shock proteins* (*Hsps*) are a class of molecular chaperones that provide high-affinity binding platforms for unfolded proteins and prevent protein aggregation, specifically during stress conditions [74]. The 26S proteasome is a multicatalytic protease responsible for ubiquitin/ATP dependent protein degradation. ROS can also modulate proteasomal dysfunction that can lead to decreased degradation of misfolded proteins, thereby resulting in the accumulation of oxidized proteins and subsequent protein aggregation. Protein aggregates can then feedback to further inhibit proteasome activities, generate additional cellular stress, and lead to cytotoxicity and human pathologies. Such phenomena have been implicated in many oxidative stress-associated disorders [75].

6. Mitochondrial dysfunction and aging

Biological aging can be defined as the gradual deterioration of biological functions of an organism related to resist stress, damage or disease, and is considered as a major risk factor for many diseases. It is a multifactorial process determined by both genetic and environmental factors. Because of its significant value from the clinical point of view, understanding the aging process is one of the biggest challenges for the biomedical researchers. Several theories have been proposed to explain the process of aging, out of which Harman's free radical/mitochondrial theory of aging is the most widely accepted [76]. It postulates that free radical reactions (FRRs) are the ultimate culprits in the progressive deterioration of biological systems that accompanies aging. Because the initiation of FRRs by mitochondria increases with age, and lifespan is determined by the rate of free radical damage to mitochondria, the theory was subsequently renamed as the “mitochondrial free radical theory of aging”. According to this theory, interventions that decrease FRRs (e.g., antioxidants such as vitamin E) or their rates of initiation (e.g., minimizing copper, iron, and other oxidant catalysts) attenuate oxidative stress and ultimately decelerate aging and the onset of age-related diseases. The cumulative damage due to oxidative stress to cellular macromolecules, such as DNA, protein, and lipids ROS during the course of life will ultimately lead to aging. As discussed earlier, mitochondria are the major source of ROS in the cell, and hence, the vicious cycle between mitochondrial dysfunction and ROS production can play crucial roles in aging and disease progression [77].

Interestingly, the modest inhibition of mitochondrial respiration in *Caenorhabditis elegans* increased the lifespan of the organism [78,79]. The study showed that *clk-1* and *isp-1* mutants reduce oxidative phosphorylation capacity and promote longevity. *Clk-1* gene is required for the biosynthesis of ubiquinone (*coenzyme Q* or Q) and mutant gene affects the electron acceptor in the respiratory ETC [78]. Mutation of *isp-1* causes alteration of the encoded [Fe-S] protein, which is in complex III of the ETC [79]. These findings prove that impairment of ETC extends the lifespan. Alteration of mitochondrial oxidative phosphorylation promotes aging. Consistently, mice with mildly reduced oxidative phosphorylation exhibited improved glucose homeostasis and lived longer [80].

In fact, during the course of evolution, several defense mechanisms have been developed in eukaryotic cells, such as enzymatic systems comprising catalase, glutathione reductase, glutathione peroxidase and superoxide dismutase (SOD) to convert ROS into non-toxic forms. However, their activity decrease as cells age, leading to a net accumulation of oxidative damage/ROS. Altered mitochondrial function is a common feature seen in multiple aspects of aging. In addition, reduced respiratory capacity and increased oxidative stress associated with aging have been reported in several regions of the brain [24]. Despite the wide popularity of the free radical theory of aging, evidence from studies on diverse model organisms still continues to accumulate in support and against its postulates. For example, over-expression of SOD in *Droshophila melanogaster* was demonstrated to have beneficial effects

and extended the life span [80]. Similarly, over-expression of the mitochondrial-targeted catalase in mice demonstrated increased life span and also exhibited a reduction in ROS levels and oxidative damage and age-associated pathologies [81]. On the other hand, mice expressing mitochondrial polymerase with defective proofreading activity exhibited accumulation of mitochondrial mutations along with premature aging; however, no increase in ROS generation was reported [82]. Similarly, deletion of mitochondrial *SOD2* extended the life span and increased ROS generation in *C. elegans* [83]. According to such differential findings, low levels of mitochondrial ROS might actually have beneficial effects, acting as signal molecules, and promoting the cells to undergo a state of higher stress resistance with extended life span [84–85] through mitohormesis [86]. Overall, these studies suggest a complex relationship between aging and ROS, which need to be unraveled.

7. Mitochondrial dysfunction and age-related neurodegenerative diseases

The brain is an energy-demanding organ that consumes > 20% of the total energy produced by an organism, and a mature brain requires > 50% of the brain's energy consumption to maintain synaptic homeostasis and plasticity. Given the high-energy requirement of the brain as well as muscles, mitochondrial diseases frequently manifest with neuromuscular abnormalities. Mitochondrial function is extremely vital for the proper functioning of the neurons because they are metabolically very active and do not have a backup system as in other cells for energy production [87]. ROS are one of the most common agents responsible for mitochondrial dysfunction. ROS hinder the function of many vital mitochondrial enzymes, such as pyruvate dehydrogenase and cytochrome oxidase [24]. ROS can harm the neuron by causing damage to the membranes, proteins, and nucleic acids. ROS not only cause damage to the mitochondria but also initiate apoptosis and programmed cell death. Because apoptosis is a systematic process of the cell and occurs only when the cell loses its self-repairing ability, dysfunctional mitochondria can trigger apoptosis, particularly through the opening of the mitochondrial permeability transition pore (MPT) located on the inner membrane of the mitochondria. This occurs after the opening of permeability transition pore (PTP), which contains VDAC, ANT, cyclophilin D, and other molecules [88]. During mitochondrial dysfunction, MPT leads to the induction of pro-apoptotic proteins, which activate a series of caspase proteolytic enzymes. Subsequently, it involves an increase in ROS, reduction in ATP production, and an associated rise in calcium, inducing apoptosis [89]. Mitochondrial dysfunction also stimulates necrosis, an accidental type of cell death, which occurs in a calcium-dependent manner [90].

Other than ROS, mitochondria can become dysfunctional through mutations accumulated over a person's lifetime. Several “large scale deletions or point mutations” have been reported in the mtDNA that adversely affect mitochondrial function by negatively affecting the energy production processes [24]. Hence, less ATP will be produced as some of the mitochondria get dysfunctional, thereby affecting oxidative phosphorylation in the cell with fewer processes operating in the cell, including autophagy and lysosomal degradation, which cause accumulation of waste products in the cell. In addition, lack of ATP in the cell affects the performance of the normal cell-to-cell communication via the synapses [91]. This is a vital function of the nervous system as it maintains the communication between the brain with the rest of the body and the external environment. Such a loss of vital information leads to visible signs and progressive pathology of neurodegenerative disease. In addition, mitochondrial dysfunction elicits the accumulation and aggregation of proteins in several ways. Studies have shown that protein accumulation can also be induced within the mitochondria. For example, in AD, the amyloid precursor protein has been shown to accumulate within the protein channels of the mitochondria, thereby causing damage to the cell [92]. Similar studies have revealed an array of proteins in various neurodegenerative diseases, demonstrating that protein accumulation inside the mitochondria can lead to dysfunction and eventual destruction of the neurons [93]. Hence, mitochondrial dysfunction has been regarded as the major contributor of neuronal degeneration [18] and is responsible for the development of several age-related neurodegenerative diseases, such as AD, PD, HD, and ALS. Accumulation of misfolded or damaged proteins within neurons is the hallmark of most age-related neurodegenerative diseases [94]. The main mitochondrial defects associated with these genes are represented in Fig. 8.

7.1. Alzheimer's disease

AD is the most common type of dementia and is one of the most progressive neurodegenerative diseases. AD is highly prevalent among the old age persons (> 65 years old); with an estimated 5.7 million people of all ages living with AD in 2018, of which, an estimated 5.5 million people of > 65 years old and approximately 200,000 individuals under age 65 exhibiting AD, though there is a certain degree of uncertainty about the younger-onset estimate [95–96]. It is marked by the severe loss of the neurons in the brain that leads to the loss of memory [97]. Two major players are often involved in its progression: plaques and tangles. Increased accumulation of extraneuronal amyloid plaques, derived from the proteolytic processing of the amyloid precursor protein (APP) and intraneuronal neurofibrillary tangles (NFTs), formed by hyperphosphorylated tau protein (pTau) are mostly observed in the brain cells of AD patients [98]. Plaques consist of amyloid beta (Aβ) fibrils that assemble from monomeric and oligomeric intermediates, and are prognostic indicators of AD. In fact, the early stage of AD is diagnosed by morphologically and functionally impaired mitochondria prone to excessive formation of ROS, resulting in the decrease of brain energy because of the reduction of ATP [99]. Accordingly, mitochondria isolated from the brain samples of AD patients exhibit altered citric acid cycle enzyme functions, including reduced pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase (KGD) activity and increased succinate dehydrogenase and malate dehydrogenase activity. Astrocytes play crucial roles in brain energy storage and immune response [100]. Astrocytes isolated from AD cases exhibit varied expression of mitochondrial-encoded genes, including tRNA *methyltransferase 61B*, *FAST kinase domains* 2, and *NADH dehydrogenase* (ubiquinone) 1 *alpha subcomplex 4-like 2*, as well as immune system associated genes, such as *clusterin*, *complement C3*, and *CD74*. Such immune response-related genes play important roles in amyloid-β generation [101]. Aβ, once formed, can communicate with the mitochondria and cause further mitochondrial abnormalities. Aβ suppresses complex IV and KGD, and binds Aβ-binding alcohol dehydrogenase (ABAD). Both KGD and ABAD produce ROS. Mitochondria have also been reported to contain active γ-secretase complexes, which are involved in cleaving APP to form Aβ and contain presenilin 1 that is encoded by PSEN 1 gene, which increases the proteolytic activity of HTRA2 serine peptidase toward inhibitors of apoptosis (IAPs). The non-soluble APP can affect outer mitochondrial membrane and interfere with protein shuttle import [99]. Impaired crosstalk between ER and mitochondria also seem to play an important role in AD pathogenesis. Upregulation of the mitochondrial-associated ER membrane proteins, such as phosphofurin acidic cluster sorting protein-2 and the σ1 receptor, which are important for neuronal survival, have been documented in AD [102]. In addition, mitochondrial dysfunction and apoptosis associated with amyloid-β-mediated toxicity have been proposed to be mediated by VDAC1 [103]. Oxidative stress might seriously damage the brain via several interacting mechanisms, including an increase in intracellular free Ca^{2+}, release of excitatory amino acids, and neurotoxicity [24]. Considerable ROS formation increased by the ETC within the mitochondria under stressful conditions and in aging constitutes a risk for developing AD. Hence, mitochondria function as both the source and target of toxic ROS because

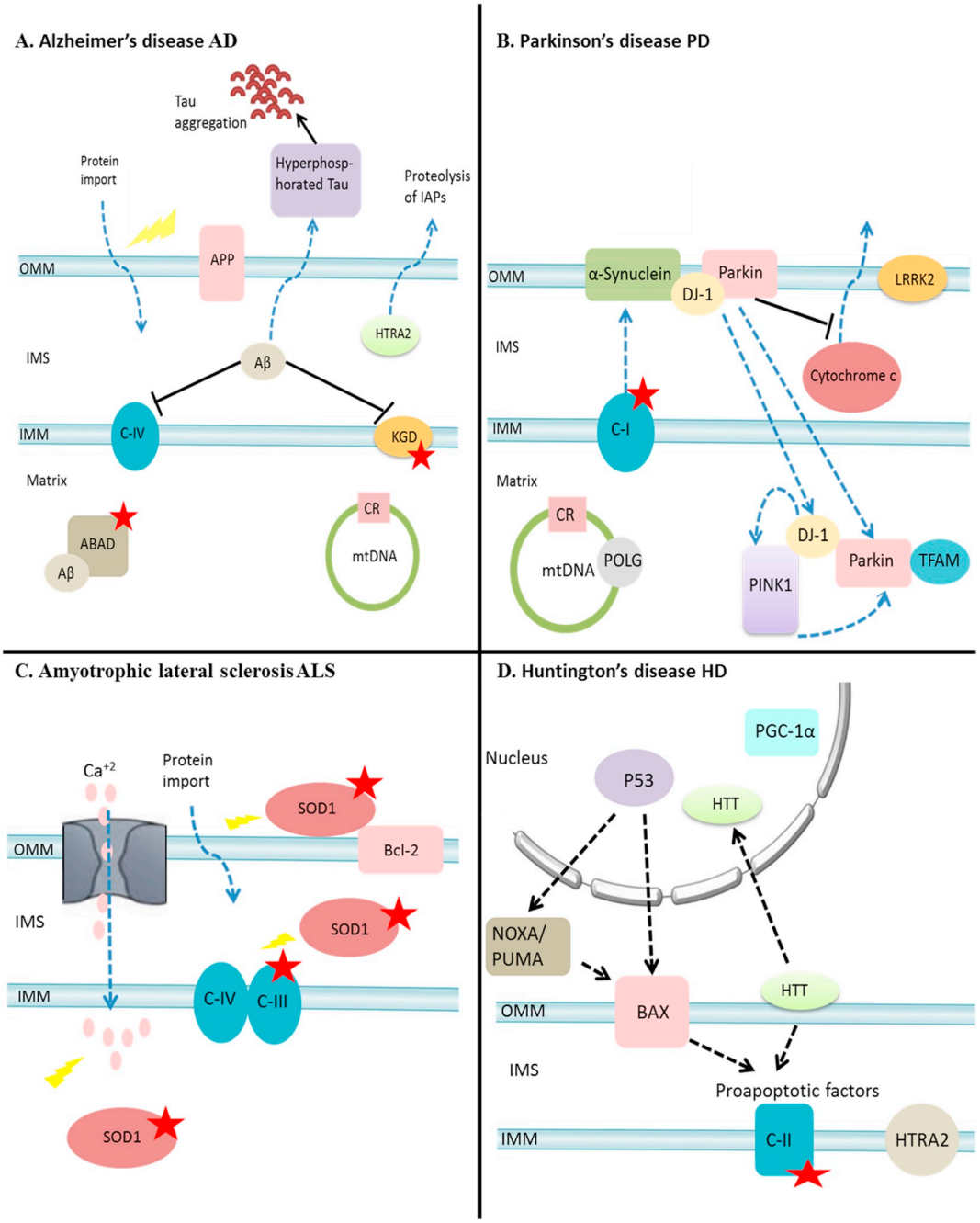

Fig. 8. The role of mitochondria in age-related neurodegenerative diseases. (A) In AD, generation of ROS (Red stars) and inhibition of energy metabolism induce the enhancement of amyloid beta (Aβ) levels in the cells, and Aβ can alter the mitochondrial function. Aβ affects the activity of complex IV (C-IV) and α-ketoglutarate dehydrogenase (KGD) and binds Aβ-binding alcohol dehydrogenase (ABAD). The amyloid precursor protein (APP) can also impair mitochondrial protein import and increase the proteolytic activity of high-temperature requirement protein A2 (HTRA2), which can lead to the cleavage of IAPs (inhibitors of apoptosis) and cell death. Outer mitochondrial membrane (OMM), intramembrane space (IMS), inner mitochondrial membrane (IMM). (B) Complex I (C-I) activity is reduced in PD. Mutations in mtDNA-encoded complex I subunits, 12SrRNA, and polymerase γ (POLG) also cause Parkinsonism. Many proteins, including the Lewy-body associated protein α-synuclein, the protein deglycase (DJ-1), Parkin, and the kinase (LRRK2), partially or fully localize to mitochondria and are associated with PD. (C) Increased expression of mutant SOD1 in ALS alters the activity of ETC and decreases mitochondrial calcium-loading capacity. Mutant SOD1 promotes aberrant mitochondrial ROS production and forms aggregates that may clog the OMM protein importation machinery or bind and sequester the antiapoptotic protein Bcl-2. (D) Complex II activity is decreased in the HD brain. Overexpression of complex-II subunits reduces cell death in striatal neurons expressing mutant HTT. Mutant HTT can also increase the -sensitivity to calcium induced cytochrome *c* release or translocate to the nucleus to affect the expression of genes associated with apoptosis.

mitochondrial dysfunction and oxidative stress are important in age-related neurodegenerative diseases, particularly AD [104]. In addition, metals such as copper is a potent mediator of highly reactive hydroxyl radical ($OH^{\bullet}$), and can subsequently contribute to the increase in oxidative stress characteristic of AD brain [105].

7.2. Parkinson's disease

PD is a neurological locomotory disorder with rigidity, bradykinesia, and resting tremor. The incidence of PD ranges from 10 and 50/100,000 persons, and its prevalence ranges between 100 and 300/100,000

population. PD frequency increases sharply with age, with its incidence and prevalence increasing progressively after age 60 [106,107]. Some acceptable etiologies of PD are mitochondrial dysfunction, oxidative imbalance, chronic inflammation, aberrant protein folding, and abnormal protein aggregation, besides certain genetic and environmental factors. The hallmark clinical manifestation of PD is pronounced reduction of dopamine, because of the loss of pigmented dopaminergic neurons in the SN [108]. Oxidative stress generated by the dopamine neurons is thought to play an important role in dopaminergic neurotoxicity. Several factors could be responsible for the oxidative stress in the dopaminergic neurons, such as DA metabolism, mitochondrial dysfunction, and neuro-inflammation, which are the manifestations of free radical/ROS generation [109]. Among these, mitochondrial dysfunction in case of PD is the most significant contributor and is associated with dysfunctional complex I of the mitochondrial ETC, which was detected accidentally upon exposure to the synthetic drug 1-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) [110]. The MPTP metabolite, 1-methyl-4- phenylpyridinium (MPP +) is selectively absorbed by pigmented dopaminergic neurons, where it suppresses NADH dehydrogenase, resulting in ROS formation and leading to oxidative stress-triggered neuronal death. Accordingly, rotenone is one of the complex I inhibitors that is used to create many PD animal models [111]. Several nuclear-encoded genes mutated in hereditary PD usually involve mitochondrial function, and mutations in such genes may lead to mitochondrial abnormalities [112]. Moreover, high levels of mtDNA deletions have been observed in SN neurons of PD patients, possibly responsible for significant respiratory chain dysfunction. Mutations in mitochondrial Pol-γ have been linked to mtDNA deletions in PD [113]. For examples, loss-of-function mutations in Parkin and *PINK1* have been reported to contribute to mitochondrial dysfunction, neurotoxicity, and early-onset PD [114]. Parkin associates with outer mitochondrial membrane and provides a protective effect against the release of cytochrome *c*. It might also associate with TFAM and enhance mitochondrial biogenesis. Hence, loss of Parkin leads to the impairment of such functions. The mitochondrial kinase, PINK1 has a protective effect against cell death, which is the result of PD-related mutations or kinase inactivation [114]. Several other genes associated with PD also contribute to mitochondrial disease. α-Synuclein immunostaining was observed in degenerating mitochondria obtained from mice overexpressing A53T α-synuclein. The overexpression of α-synuclein negatively affects mitochondrial function and increases the toxicity of MPTP. When oxidized, the protein deglycase (DJ-1) translocates to mitochondria (IMS and matrix), down-regulates the PTEN-tumor suppressor, and protects the cell from oxidative-imbalance-induced cell death. Induction of permeability transition, impaired intracellular calcium homeostasis, and oxidative stress occur in the affected cells and lead to necrosis or apoptosis, depending on the rate of consumption and depletion of ATP. Physical associations have been reported between DJ-1 and α-synuclein, DJ-1 and parkin, and DJ-1 and PINK1; and there is genetic evidence that DJ-1, PINK1, and parkin function sequentially in the same pathway. About 10% of leucine-rich repeat kinase 2, LRRK2 is localized in the mitochondria, and PD-related mutations augment its kinase activity. LRRK2 is a large, widely expressed, multi-domain and multifunctional protein. LRRK2 mutations are the major cause of inherited and sporadic PD [115]. A mutation in the mitochondrial serine peptidase high-temperature requirement protein A2 (HTRA2) 2 was recorded in 1% of sporadic PD individuals. Overexpression of the mutant altered normal HTRA2 protease activity, and HTRA2 knockout resulted in striatal degeneration and Parkinsonism. Furthermore, creatine, which is a nitrogenous guanidine compound forming high energy phosphate bonds, and naturally found in vertebrates, serving as an energy supplier to muscle and nerve cells, also possesses antioxidant properties and acts as an effective inhibitor for mitochondrial permeability transition pore opening and mitochondrial iron accumulation. Creatine successfully restored MPTP-induced loss of dopamine and protected dopaminergic neurons in MPTP mouse model of PD [116].

7.3. Huntington's disease

HD is a rare, inherited, and an autosomal, fatal neurodegenerative disease with cognitive problem and motor impairment caused by the accumulation of insoluble polyglutamine, with a prevalence rate of 2.71 per 100,000 persons [117]. Generation of oxidative stress because of the accumulation of ROS is thought to be one of the key players of HD pathogenesis. Transition metals (e.g. Fe, Cu, Zn), one of the components of ROS, exhibit the dynamic property of sharing electrons easily, because of the presence of unpaired electrons in their outermost orbital shell, and can take part in a number of physiological redox reactions [118]. Previous studies have suggested metal dyshomeostasis to be a major contributor to HD pathogenesis. In particular, Fe and Cu have been implicated as mediators of HD pathology and have been shown to accumulate in the post-mortem brain tissues of HD patients, R6/2 mice, and in a *Drosophila* model of HD [119–120]. Repeated sequences of cytosine-adenine-guanine (CAG) in the DNA translated into glutamine triplet repeats in huntingtin (*Htt*) gene or *HD* gene are specifically found in HD patients [121]. A recent MRI study showed the enhanced accumulation of FE in the basal ganglia and cortex of human HD patients and found its correlation with the CAG repeat number and severity of the disease pathogenesis [120]. Several studies strongly correlated the impairment of mitochondria in HD pathogenesis [122]. Both synaptic and non-synaptic mitochondria sampled from a mouse model of HD showed ameliorated calcium influx [123]. Mitochondrial fission plays a crucial role in the pathogenesis of HD; the interaction of mutated mt(Htt) with Drp1 has been found to enhance the GTPase activity of Drp1, resulting in excessive mitochondrial fragmentation and abnormal distribution, leading to defective axonal transport of mitochondria and selective synaptic degeneration. Hence, Drp1 might represent a therapeutic target to neurodegeneration in HD. Induction of calcium stress in the striatal and cortical neurons expressing mtHtt has been observed to reduce mitochondrial calcium uptake, increase ROS generation, enhance mitochondrial depolarization, and induce apoptosis through the opening of mitochondrial permeability transition pore (PTP) [124]. Mutant HTT also associates with the outer mitochondrial membrane and increases the sensitivity to calcium-induced cytochrome *c* release. Mutant HTT also translocates to the nucleus, where it binds and increases the level and transcriptional activity of p53. P53 activates the pro-apoptotic protein BAX, either directly or by increasing the expression of Bcl2 homology domain 3 (BH3)-only Bcl-2 family members, NOXA, and PUMA [125]. Genetic elimination of PGC-1α controls the progression of HD [126]. Activation of PPAR- γ receptors can enhance mitochondrial dysfunction in mHtt-expressing cells that can have a significant role in HD pathogenesis. Therefore, PPAR- γ agonist has a protective effect against oxidative stress and attenuate mitochondrial dysfunction in mHtt striatal cells. Thus, mitochondrial biogenesis pathway serves as a potential therapeutic target for HD medication [127].

7.4. Amyotrophic lateral sclerosis

ALS is the loss of upper or lower motor neurons in the spinal cord and brain, which leads to fatal paralysis. The incidence of ALS is approximately 1–2.6 cases per 100,000 persons annually, whereas the prevalence is approximately 6 cases per 100,000 [128]. Oxidative stress, which occurs because of the generation and accumulation of ROS, is one of the major contributors to ALS pathology and affects the presynaptic transmitter releasing machinery. In ALS mouse models, nerve terminals have been shown to be sensitive to ROS, suggesting that oxidative stress, along with compromised mitochondria and increased intracellular Ca^{2+} enhances the presynaptic decline in neuromuscular junctions. This initial dysfunction is followed by the neurodegeneration induced by inflammatory agents and eventual loss of trophic support [129]. Mutation in the Cu/Zn *SOD1* gene encoding the antioxidant enzyme SOD is a major manifestation of ALS. Mutated SOD1 binds to

the apoptotic regulator Bcl-2, alters VDAC conductivity, reduce ATP production, and increases calcium accumulation. Such alterations lead to elevated mitochondrial potential and enhanced oxidative species production [130]. In ALS patients, mitochondrial impairments of the skeletal muscle are associated with a reduction in the transcription of PGC-1a and PGC-1b, NRF1, ERRa, Mfn1 and Mfn2, and the protein content as well as increases in several miRNAs that are possibly involved in neuromuscular junction and skeletal muscle regeneration. These results suggest that mitochondrial dysfunction in the skeletal muscle contributes to the pathogenesis of ALS [131]. Moreover, PPAR-γ might be the main signaling pathway contributing to neuroinflammation, which is considered as one of the hallmarks of ALS. Hence, neuroinflammation blockage might have an effective therapeutic function on ALS patient [132]. Increase in the oxidants inside the cell leads to protein carbonylation and tyrosine nitration. Accumulation of damaged proteins occurs in the CNS of ALS patients. This accumulation interferes with the axonal transport and anterograde and retrograde transport of mitochondria to the nerve terminal, thereby reducing ATP production and synaptic transmission by altering calcium signaling [133]. Enhancing mitochondrial biogenesis by AMPK activation might have a promising therapeutic approach in the mice model of ALS [134]. Recently, it was also reported that the activation of SIRT1 enhances the survival of motor neurons by enhancing PGC-1a in the transgenic mice model of ALS [135]. Collectively, these observations strongly indicate that PPAR-γ transcriptional activity within the CNS may help to control the progression of ALS [136].

8. Therapeutic strategies against mitochondrial dysfunction

The principal cause of mitochondrial disease lies in the genetic range and clinical complexity owing to mutation(s), heteroplasmy (concurrent presence of normal and mutant genes), age, and the environment. These reasons have pushed the researchers to develop compounds/processes for targeting the crucial pathways that regulate mitochondrial biogenesis, fission and fusion, mitochondrial autophagy (mitophagy), heteroplasmy shift, and induction of antioxidant mechanisms. Some of the compounds and approaches used for targeting mitochondria are discussed below:

8.1. Lifestyle interventions

8.1.1. Exercise

Exercise enhances the physical capacity and quality of life in individuals by improving mitochondrial function, and getting rid of unhealthy mitochondria. Continuous exercise triggers various signaling pathways related to biogenesis of mitochondria, dynamics, and metabolism. During exercise, skeletal muscles generate free radicals and ROS owing to vigorous activity. Muscle fibers, such as type I and type II skeletal muscle fibers possess unique properties that promote mitochondrial ROS production [137]. However, several other tissues such as the heart, lungs, or white blood cells might significantly contribute to the total ROS generation within the body under certain circumstances. Studies have documented that the normal metabolic changes, such as the increased release of catecholamines during exercise might play an important role in increased ROS formation. Exceptionally, heavy to very heavy exercise might induce muscle damage, thereby, leading to inflammatory processes that can eventually lead to the excessive production of free radicals/ROS. Thus, moderate exercise will assist in controlling the level of ROS generation, and can hence render better health characteristics [138]. Several studies have also reported that lifestyle routine assists in maintaining the youth and prolong the development of age-related diseases. Exercise therapy improves mitochondrial function by enhancing oxidative phosphorylation activity [139]. Wenz et al. reported the benefit of exercise in *COX10* knockout mice, which exhibited delay in disease onset, increased ATP levels, oxidative phosphorylation activity, and life expectancy [140]. Because aging is accompanied with the loss of muscle mass and structural changes in neuromuscular components, exercise can promote beneficial adaptations, which can prevent the progression of loss of function of aged muscles [141].

8.1.2. Diet

Dietary intervention can lead to the improvement in the mitochondrial health in different ways [142]. Caloric restriction (CR) has been reported in the reduction of ROS and extending the longevity of several laboratory mice, hamsters, dogs, fish, invertebrate animals, and yeast models. CR retards aging and senescent, thereby improving the longevity of an organism. Additionally, CR is known to enhance the ability to repair oxidatively damaged DNA and to replace damaged proteins [143]. On the contrary, some studies have reported that CR can also mediate mito-hormesis, and can enhance the production of ROS, thereby activating stress response pathways, and eventually increasing the lifespan of organisms [144]. Researches have shown that CR mainly activates the Nrf2/ARE pathway, which might serve as an endogenous antioxidant system within the vasculature, thereby increasing the tolerance to cellular oxidative stress. Induction of quinone reductase, NQO1 by resveratrol in human K562 cells involves the antioxidant response element ARE and is accompanied by nuclear translocation of transcription factor Nrf2 [145]. Several currently proposed CR mimics are phytochemicals (resveratrol, quercetin and curcumin) that act mainly/partly through the activation of Nrf2 pathway, and ultimately leading to increased life-span [146]. Furthermore, proper adjustment of the quantity and quality of calories in taken at a daily basis is important for the patients with mitochondrial dysfunction as well as for normal individuals. Ketogenic diet (KD), with high fat and low glucose level enhances lipid utilization by mitochondrial beta oxidation and ketone body production in the liver [140]. Studies also showed that KD improves brain energy metabolism by stimulating mitochondrial biogenesis, suppressing ROS production, increasing neuron glia interaction and enhancing ATP production [147]. Many epidemiological studies have shown that nutritional status of an individual is one of the important factors that play an important role in aging and neurodegenerative diseases [148].

8.2. Pharmacological strategies

Generation of excessive ROS leads to structural and functional abnormalities in the mitochondria that can exacerbate mitochondrial dysfunction, thereby leading to disease. In this context, pharmaceuticals that maintain mitochondrial homeostasis could potentially improve the mitochondrial health in a wide range of diseases. Many strategies are currently being employed to limit the altered mitochondria, such as targeting ROS formation, mitochondrial biogenesis, mitochondrial dynamics, mitochondrial protein import, and mtDNA import.

8.2.1. Targeting ROS

Studies have reported that the pathogenesis of mitochondrial diseases is associated with altered antioxidant defense or excessive generation of ROS, resulting in irreparable damage to macromolecules. Because neurodegenerative diseases are very complicated and have multifactorial etiologies, wherein oxidative stress and mitochondrial dysfunction are involved, the development of antioxidants targeting these factors could potentially assist in the treatment of these disorders [149]. For example, mercaptamine is proposed to increase the levels of glutathione that acts as an antioxidant to combat ROS produced by damaged mitochondria in mitochondrial disease patients. Similarly, vatiquinone is also an antioxidant, which has been shown to be beneficial in clinical trials [150]. RTA-308 is an antioxidant and anti-inflammatory agent that acts by increasing the activity of Nrf2, which in turn enhances the expression of pro-oxidant genes and represses inflammatory gene expression in animal models [151]. Bendavia is a

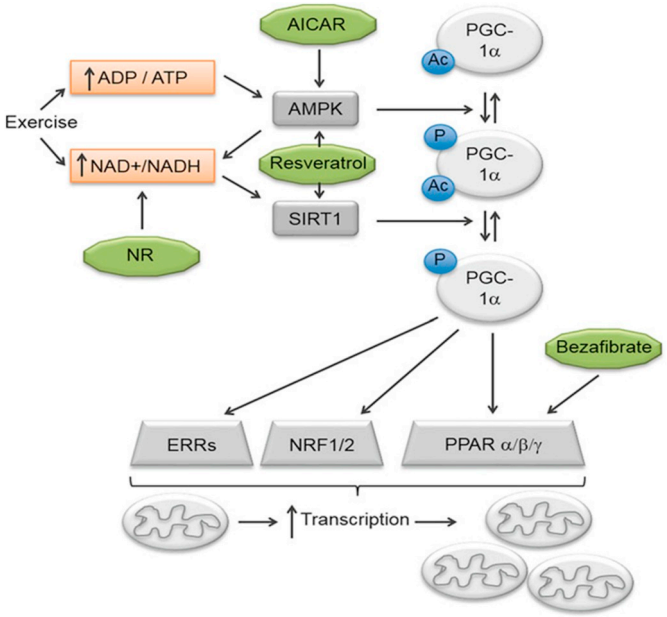

Fig. 9. Multiple pathways showing the mitochondrial biogenesis and energy expenditure are depleted during energy expenditure. The increase in the ADP/ATP ratio owing to the depletion of ATP and NADH during energy expenditure is perceived by AMPK that activates PGC-1α. Then, AMPK affects the NAD^+/NADH ratio via NAMPT (not shown), which regulates the deacetylase SIRT1 that fully activates PGC-1α. Subsequently, PGC-1α interacts with transcription factors and enhances the transcription of nuclear-encoded and mitochondrial-encoded mitochondrial genes; including estrogen related receptor (ERR), nuclear respiratory factor (NRF), and peroxisome proliferator-activating receptor (PPAR). The compounds shown in green denote the stimulators of this pathway.

peptide that prevents cardiolipin from converting cytochrome *c* into a peroxidase, while rendering its electron transport chain function intact [152]. Moreover, antioxidants such as ebselen, coenzyme Q, lipoic acid, and green tea polyphenol Epigallocatechin gallate (EGCG) were found to exert some beneficial effects in MPTP-induced animal models of neurodegenerative diseases [153–156]. A similar effect was observed using melatonin, which acts as a mitochondria-targeted antioxidant and has protective actions similar to the synthetic antioxidants [157,158]. AD patients exhibited low levels of melatonin in their ventricular system, which was accompanied by mitochondrial damage. The mechanisms by which melatonin has been proposed to play beneficial roles in AD include its antioxidant activity, anti-amyloidogenic activity, and the inhibition of tau hyperphosphorylation [159]. Nanoparticle formulations capable of encapsulating therapeutic molecules and targeting specific transport processes in the brain vasculature are potential tools for enhancing drug transport through blood brain barrier in neurodegenerative/ischemic disorders and targeting relevant regions in the brain for regenerative processes. Ceria nanoparticles, which are strong and recyclable ROS scavengers, were found to localize in the mitochondria and suppress neuronal death in a 5XFAD transgenic AD mouse model [160]. This effect was attributed to the ability of nanoparticles to mitigate reactive gliosis and morphological damage to mitochondria.

8.2.1.1. MitoQ. MitoQ (mitoquinone) is a well-known, extensively used antioxidant for targeting mitochondria. Researchers have shown that MitoQ mainly accumulates inside the matrix-facing surface of the inner mitochondrial membrane, with the ubiquinone component penetrating deeply into the hydrophobic interior of the membrane [161]. MitoQ is a promising neuroprotective compound because of its direct antioxidant action. CoQ10 and MitoQ are promising neuroprotective compounds, which continuously scavenge peroxyl, peroxynitrite, and superoxide, thereby protecting the mitochondria against lipid peroxidation. MitoQ also possess simultaneous anti-inflammatory and anti-hypoxic properties, and owing to redox cycling of quinone and generation of superoxide, it may become pro-oxidant and proapoptotic. Several diseases other than neurodegenerative disease involving oxidative stress, such as ischemia-reperfusion [162], fatty liver disease [163], hypertension [164], kidney damage in type I diabetes [165] and sepsis [166] are protected by MitoQ as demonstrated in animal models.

8.2.1.2. CoQ10. CoQ10 (Co-enzymeQ 10) is a neuroprotective agent. Postmortem studies have shown that after the death of an organism, CoQ10 (mainly oxidized CoQ10) levels in the plasma and platelets of neurodegenerative patients significantly decreases compared to age matched controls, thereby suggesting that intake of CoQ10 supplements may be beneficial. In particular, paraquat- and rotenone- induced mitochondrial dysfunction and neurodegeneration in rat mesencephalic primary neurons were inhibited by CoQ10 [167]. Processing of neuronal cells with CoQ10 maintains the mitochondrial membrane potential during oxidative stress and reduces the generation of ROS by the mitochondria, which ultimately protects from disease onset.

8.2.1.3. Antioxidant vitamins. Several vitamins act as antioxidants and have been tested for their neuroprotective efficacy. Deficiency of vitamin E increased MPTP-induced dopaminergic neurotoxicity [168]. Several studies in humans suggest that the administration of a combination of high-dose of vitamin E and vitamin C supplements was associated with the reduced progression of PD [169]. However, the results of double-blind, randomized controlled trials are discouraging, because they showed vitamin E has no benefits on PD. The protective role of vitamin C in PD remains controversial because one epidemiological study reported a decreased risk of PD in individuals consuming vitamin C rich diet, whereas other studies showed no effects or even an increased risk of PD upon vitamin C consumption [170].

8.2.2. Targeting mitochondrial biogenesis

8.2.2.1. Proliferator-activated receptor γ coactivator 1 (PGC1)-α. This approach walks through the PGC1-α, which is the major transcriptional co-activator protein regulating the expression of nuclear mitochondrial genes. The interaction of PGC1-α with multiple transcription factors leads to the enhanced transcription of nuclear-encoded mitochondrial genes [171]. Multiple pathways of mitochondrial biogenesis demonstrate the use of both genetic and pharmacological assays in specific mouse models to target pathways using low-molecular-weight compounds, such as resveratrol, bezafibrate, and NAD^+ precursors that target sirtuin (Sirt1) and/or AMPK, and PPAR (Fig. 9). Overexpression of PGC1-α has been observed in mouse models of Duchenne muscular dystrophy (DMD), ALS, and PD. Increased mitochondrial biogenesis linked to an improvement in the phenotype was shown in some cases [172]. Overall, studies suggest that increasing PGC1-α activity can increase mitochondrial biogenesis that can have therapeutic implications in mitochondrial disease. The PGC-1α signaling pathway is related to HD pathogenesis, and common variations in the *PGC-1α* gene are associated with delayed onset of HD. Therefore, manipulating the regulatory network PGC-1α to control the metabolic state of the mitochondria is a promising HD therapy [173]. PGC-1α might also be a therapeutic target for PD [174]. PGC-1α is also critical for the control of cellular oxidative stress by regulating various antioxidant enzymes, such as SOD, catalase, and glutathione peroxidase [175]. Additionally, PGC-1α regulates ROS production via Sirt1 [176]. Therefore, the ROS scavenging activity of PGC-1α can serve as a crucial target in many age-related neurodegenerative diseases associated with oxidative stress-induced damage, such as AD and ALS [177].

8.2.2.2. Resveratrol. Resveratrol, proposed to be an activator of Sirt1, is a natural stilbenoid found mainly in the skin of grapes [178]. The expression of PGC1-α is regulated by AMPK and Sirt1 NAD^+ dependent

deacetylase. Changes in the level of NAD^+/NADH and AMPK regulate the expression of Sirt1 that are required at several steps in the Krebs cycle during oxidative phosphorylation. Although the effects of resveratrol are well documented, there are several controversies regarding its molecular mechanism. One of them is the indirect regulation of Sirt1 expression by resveratrol via AMPK, further regulating NAD^+ levels which in turn controls Sirt1 activity [179]. Simultaneously, resveratrol can act directly on Sirt1 homologues in vitro and can catalyze the deacetylation reaction of acetyl lysine [180]. Nevertheless, resveratrol increases mitochondrial biogenesis and oxidative respiration in mouse models of obesity [181]. Resveratrol has been tested in mouse models of Friedreich's ataxia, the mdx model for DMD, SOD1 ALS models, and in AD, HD, and PD models for neurological indications and mitochondrial disease [182].

8.2.2.3. Isoflavones. Isoflavone is a dietary supplement isolated from soybeans and are well-known for their antioxidant, antimicrobial, and anti-inflammatory health benefits. Isoflavones act as phytoestrogens and exert pseudo-hormonal activity by binding to estrogen receptors (ER) in mammals, in addition to possessing antioxidant, anticancer, antimicrobial, and anti-inflammatory activities. Daidzein and genistein are the most common isoflavones with a characteristic chemical structure (B-ring is linked to the C3 position of the C-ring instead of the C2 position) resembling the structure of estrogens, particularly 17-β estradiol. Hence, isoflavones induce either a weak estrogenic (agonistic) or anti-estrogenic (antagonistic) effect, depending on the levels of endogenous estrogens and ER [183]. Oxidative stress-induced apoptosis and the inhibition of cell proliferation can be prevented by soy isoflavones via the regulation of ERβ and Bcl-2/Bax expression and modulation of cell survival signaling pathways, such as the PI3K pathway [184]. Isoflavones initiate mitochondrial biogenesis through PGC1 and increased SIRT1 activity [185], and can hence act as important players in ameliorating mitochondrial dysfunction.

8.2.2.4. Quercetin. Quercetin is an important natural polyphenolic flavonoid that is ubiquitously present in the diet comprising a variety of fruits and vegetables. For a long time, quercetin has been considered as a potent antioxidant and anti-inflammatory molecule [186]. Recent studies have suggested that quercetin might exert its beneficial effects irrespective of its free radical-scavenging properties. Quercetin assists in increasing the mitochondrial DNA copy number and messenger RNA levels of four genes related to mitochondrial biogenesis (*citrate synthase*, *cytochrome c oxidase I*, *SIRT1*, and *PGC-1α*) [187]. It also interacts with the mitochondrial membranes and influences the function of the mitochondrial membrane-located proteins. Although previous studies suggest that quercetin is thought to modulate energy production, interactions with several mitochondrial proteins, regulation of apoptosis, and the direct free radical-scavenging activity cannot be regarded as the major mechanism for the clinical effects of quercetin. Overall, quercetin triggers cell death via the activation of the intrinsic apoptotic pathway, involving the modulation of intricate cellular signaling pathways of apoptosis in different cell lines and in vivo [186].

8.2.2.5. Bezafibrate. Bezafibrate is a PPAR agonist that was initially developed for treating hyperlipidemia [188]. Recently, PPARs have been shown to regulate mitochondrial biogenesis via PGC1-α [189] and were also shown to increase the respiratory function in patient-derived cells. In addition, bezafibrates have been tested in multiple mitochondrial disease mice models with less success. ΔCox10 mice, which received 0.5% w/w dietary bezafibrate, showed increased muscle mitogenesis, delayed onset of myopathy, and extended lifespan [190]. Further studies in the Twinkle mutant "deletor" mouse and the Polg "mutator" mouse had different success rates. The "deletor" mouse demonstrated reduced mtDNA deletion load and had fewer COX-negative muscle fibers, but, at the expense of the body weight and hepatic complications. On the other hand, the Polg "mutator" mouse exhibited multiple beneficial phenotypes, including delay in hair loss, reversed of an abnormal spleen, and reduced weight loss despite not displaying an increase in mitochondrial biogenesis during bezafibrate treatment [191]. Overall, bezafibrate was partially successful in cellular and animal models by increasing mitochondrial function and ameliorating mouse model phenotypes.

8.2.2.6. NAD^+ precursors. NAD^+ precursors are recent developmental agents that can be used directly as therapeutic agents, in particular nicotinamide riboside (NR). NR has been shown to improve muscle mitochondrial performance in wild-type and high-fat diet mice. NR was subsequently used to treat the "deletor" adult-onset mitochondrial disease mouse in two dosing schedules representing pre- and post-disease onset situations (400 mg/kg/day), and was seen to be beneficial in both dosing situations, increasing intracellular NAD^+, increasing mitochondrial biogenesis, and reducing the accumulation of damaged mtDNA [192]. Therefore, increasing the concentration of NAD^+ can be of great potential for treating mitochondrial dysfunction.

8.2.3. Targeting mitochondrial dynamics

As described earlier, cells use three different strategies to deal with mitochondrial dysfunction: (1) mitochondrial fission that segregates damaged mitochondria to mark them for degradation, (2) mitochondrial fusion that allows functional mitochondria to complement dysfunctional mitochondria by diffusion and sharing of components between organelles, and (3) mitophagy that selectively degrades damaged mitochondria. The complex interplay among these processes is important for maintaining mitochondrial homeostasis, and hence, has an important role in many mitochondria related diseases [193].

Mitophagy can be induced by altering the mitochondrial membrane potential utilizing mitochondrial uncouplers, such as FCCP/CCCP, or agents that alter mitochondrial respiration, such as antimycin A and oligomycin [194]. Moreover, iron chelators have been reported to induce mitophagy in PD patients in the PINK1/Parkin-independent manner [195]. PINK1/Parkin plays a crucial role in mitophagy; therefore, recent studies have focused on identifying and developing compounds that enhance PINK1-Parkin function to induce cell death. Kinetin, a precursor of ATP analog kinetin triphosphate, which induces the activity of wild-type and PD-related mutant PINK1, recruiting Parkin to the damaged mitochondria and reducing mitochondria-induced apoptosis that reduce excessive fission [196], assists in maintaining mitochondrial integrity and neuronal function. Other promising agents for maintaining mitochondrial turnover and neuronal function in oxidative stress- and mitochondrial-related disorders are Mdivi-1, Dynasore, and P110. Mdivi-1 prevents mitochondrial division by selectively inhibiting dynamin, a component of the mitochondrial division apparatus. Mdivi-1 reduces the permeability of mitochondrial outer membrane and subsequent cytochrome *c* release, thereby decreasing the rate of apoptosis [197]. Dynasore is a small molecule inhibitor of endocytic pathways that reduces the activity of dynamin 1, dynamin 2, and Drp1 [198]. Dynasore protects mouse cardiomyocytes by reducing oxidative stress-induced mitochondrial fragmentation, maintaining mitochondrial morphology, and restoring cellular ATP levels. P110 is a peptide inhibitor of excessive mitochondrial fission that inhibits Drp1 activity and blocks the interaction between Drp1 and FIS1, another protein involved in mitochondrial division. P110 was found to reduce ROS generation and mitochondrial fragmentation and inhibits apoptosis and autophagic cell death, thus a neuroprotective effect in a PD model [199]. Modulating mitophagy, fusion, and fission warrants future research using appropriate disease models to further unravel their therapeutic potential.

8.2.4. Targeting mitochondrial DNA transport

As outlined above, mtDNA mutations are associated with mitochondrial dysfunction and the subsequent onset and progression of several age-related neurodegenerative diseases. We now know that

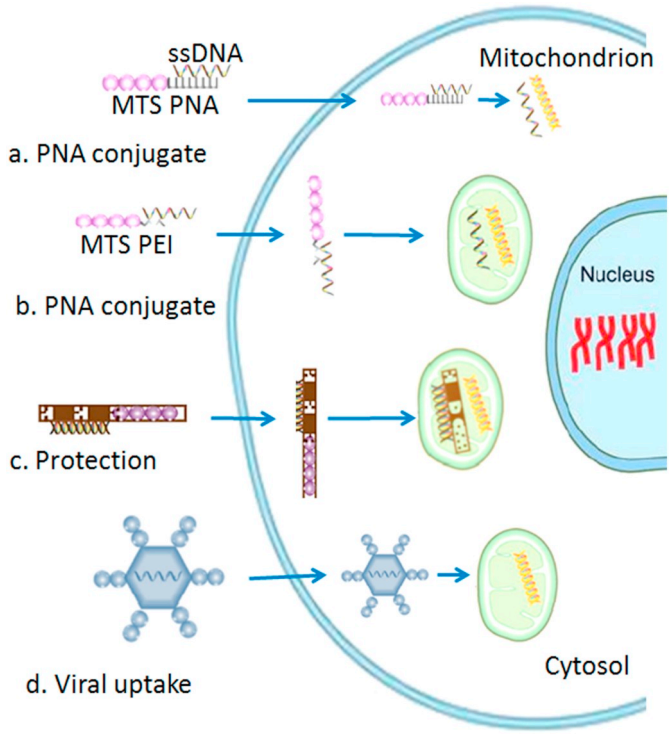

Fig. 10. Different approaches of transferring DNA into mitochondria in whole cells. DNA can be (a) annealed to a peptide nucleic acid (PNA) moiety conjugated to a mitochondrial-targeting sequence (MTS), (b) complexed with polyethylenimine (PEI) conjugated to a MTS, (c) loaded on the TFAM factor fused to a MTS and transduction domain (TD), (d) incorporated into adeno-associated virus particles carrying MTS. TFAM: transcription factor A mitochondrial, mRNA: messenger RNA, ssDNA: single-stranded DNA.

most mitochondrial proteins are encoded by nDNA and are imported to mitochondria via mitochondrial membrane translocases [25]. Specific targeting of the import of mitochondrial macromolecules to modulate the expression of mutated mtDNA or replacing impaired proteins are promising strategies for overcoming disorders associated with defective mitochondrial biogenesis and function. Mitochondrial protein import system has been typically used for introducing DNA into the mitochondrial matrix. Different approaches of transferring DNA into whole cells are shown in Fig. 10. Various attempts have been made to employ alternatives for the protein import pathway to import exogenous DNA into the mitochondrial matrix, such as “protofection”, wherein the combination of a protein transduction domain (PTD) with a mitochondrial targeting sequence (MTS) are fused to the TFAM mitochondrial transcription factor, for yielding a carrier called mitochondrial-targeting domain-TFAM. In such a system, PTD ensures transduction into the cells, MTS promotes mitochondrial targeting and import, and TFAM transports DNA [200,201]. Using this assay, the mitochondria-deficient phenotype of PD cybrids was reportedly rescued. However, the strategy suffers because of the lack of direct molecular evidence, confirming the delivery of DNA into the organelles. Alternative approaches to delivering DNA into the mitochondrial matrix include the cationic carrier DQAsome [202], liposome-based carrier MITO-Porter [203] and mitochondrial presequence polyethylenimine conjugates [204]. Transporting antisense RNA that can hybridize specifically to a mutated region into the mitochondrial matrix is a promising way to prevent replication of mutated DNA. Sequence specific peptide nucleic acids (PNAs), which have high stability and affinity toward the complementary sequences of DNA, are molecules of interest in modern gene therapy. PNA fused to a mitochondrial presequence penetrates cellular and mitochondrial membranes, and specifically inhibits the replication of mutated DNA [205]. However, subcellular trafficking and cellular uptake efficiency are the major obstacles in actively applying PNAs in gene therapy [206]. Conjugating PNAs with the lipophilic phosphonium cation is beneficial for overcoming these obstacles. This conjugate can successfully enter cells and can be transported into the mitochondrial matrix, where it selectively inhibits the replication of a DNA region with an A8344G point mutation that causes mitochondrial disease, myoclonic epilepsy, and ragged red fibers syndrome. Electroporation can be used to deliver DNA constructs in isolated mitochondria [207]; however, the conditions necessary for successful electroporation damage the structural integrity of these organelles. By contrast, exogenous linear DNA can be incorporated naturally into the matrix through mitochondrial VDACs and can serve as a template for DNA replication or promoter-mediated transcription. Overall, the approaches for delivering DNA on the mitochondria exhibit great promise for studying normal mitochondrial genome functions and mitochondria-related disease pathologies.

8.3. Mitochondrial replacement and stem cell therapy

Mitochondrial replacement therapy is a recent intervention with tremendous potential for treating mitochondrial pathologies, particularly those associated with mtDNA mutation. Unlike nDNA mutations that are generally transmitted in an autosomal recessive manner, mtDNA mutations are more severe, because they are transmitted to progeny solely from the maternal line [208]. As the name suggests, mitochondrial replacement can be achieved by transferring the nuclear genome of a cell with affected mitochondria. For example, a nucleus can be transferred from an affected oocyte into another oocyte with healthy cytoplasmic components. This therapy gives rise to a cell with healthy mitochondria without changing the nuclear genome [209], effectively avoiding the genetic transference of mtDNA mutations to the progeny. Mitochondrial replacement techniques (MRTs) include maternal spindle transfer and pronuclear transfer [208]. MRT can also be used to generate homologous stem cells corrected for mtDNA mutations. The generation of embryonic stem cells from healthy oocytes with replaced mtDNA using MRT and their subsequent differentiation into different cell types with healthy mitochondria can lead to paradigm shift in the treatment of maternally heritable mitochondria-related disorders [210]. However, the implementation of MRT for human use is still a matter concern worldwide because of safety and ethical issues related to germline modification. MRT along with stem cell therapy has the potential to be used as a crucial therapy for neurodegenerative disorders in spite of the complexity of these techniques.

9. Conclusion

Mitochondria are vital organelles of the cell. Any dysfunction in the mitochondrial leads to the pathogenesis of various disorders. Impairment and abnormality in mitochondrial biogenesis and dynamics, such as reduction of fusion and enhancement of fission are important players associated with mitochondrial dysfunction, and neurodegenerative diseases, including *Alzheimer's disease*, *Parkinson's disease*, *Huntington's disease*, and *amyotrophic lateral sclerosis*. Electron transport chain (ETC) is not only the primary source of ATP and ROS but also associated with improved lifespan in many models. Under normal physiological conditions, the cellular machinery is able to remove damaged mitochondria from the cells or induce cell death to maintain homeostasis. Altered ETC leads to the overproduction of ROS, reduction of ATP concentration, and excessive accumulation of calcium. Therefore, mitochondria are considered as potential targets for the development of therapeutic interventions targeting crucial pathways regulating mitochondrial biogenesis, fission and fusion, mitochondrial autophagy, genomic integrity, heteroplasmy shift, and antioxidant defense mechanisms to combat the progression of age-related neurodegenerative diseases. This review comprehensively characterized the different etiologies and specific therapeutic measures of

mitochondrial dysfunction in context to age-related neurodegenerative diseases. Furthermore, this review suggests the implementation of specific strategies, such as enhancing the antioxidant bioavailability via new delivery systems, identifying unique mitochondrial proteins as specific targets for the newly developed drugs, exploring the signaling pathways involved in the regulation of mitochondrial biogenesis and dynamics, and identifying and determining the most effective doses of natural products to counteract mitochondrial dysfunction-related diseases. The review also warrants more studies to be conducted for assessing the mechanisms of mitochondrial impairment using specific animal models for the identification of novel mitochondria targeted therapeutic interventions in context to age-related neurodegenerative diseases.

References

[1] R.E. Jensen, A.E. Johnson, Opening the door to mitochondrial protein import, Nat. Struct. Mol. Biol. 8 (2001) 1008–1010, https://doi.org/10.1038/nsb1201-1008.

[2] V.K. Mootha, J. Bunkenborg, J.V. Olsen, M. Hjerrild, J.R. Wisniewski, E. Stahl, M.S. Bolouri, H.N. Ray, S. Sihag, M. Kamal, N. Patterson, E.S. Lander, M. Mann, Integrated analysis of protein composition, tissue diversity, and gene regulation in mouse mitochondria, Cell 115 (2003) 629–640, https://doi.org/10.1016/S0092-8674(03)00926-7.

[3] D.J. Roberts, S. Miyamoto, Hexokinase II integrates energy metabolism and cellular protection: Akting on mitochondria and TORCing to autophagy, Cell Death Differ. 22 (2015) 248–257, https://doi.org/10.1038/cdd.2014.173.

[4] M. Liesa, M. Palacín, A. Zorzano, Mitochondrial dynamics in mammalian health and disease, Physiol. Rev. 89 (2009) 799–845, https://doi.org/10.1152/physrev.00030.2008.

[5] M. Picard, T. Taivassalo, G. Gouspillou, R.T. Hepple, Mitochondria: isolation, structure and function, J. Physiol. 589 (2011) 4413–4421, https://doi.org/10.1113/jphysiol.2011.212712.

[6] J.R. Friedman, J. Nunnari, Mitochondrial form and function, Nature 505 (2014) 335–343, https://doi.org/10.1038/nature12985.

[7] A.S. Rambold, B. Kostelecky, N. Elia, J. Lippincott-Schwartz, Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation, Proc. Natl. Acad. Sci. U.S.A. 108 (2011) 10190–10195, https://doi.org/10.1073/pnas.1107402108.

[8] L.C. Woods, G.W. Berbusse, K. Naylor, Microtubules are essential for mitochondrial dynamics-fission, fusion, and motility-in dictyostelium discoideum, Front. Cell Dev. Biol. 4 (2016) 19, https://doi.org/10.3389/fcell.2016.00019.

[9] S. Anderson, A.T. Bankier, B.G. Barrell, M.H.L. de Bruijn, A.R. Coulson, J. Drouin, I.C. Eperon, D.P. Nierlich, B.A. Roe, F. Sanger, P.H. Schreier, A.J.H. Smith, R. Staden, I.G. Young, Sequence and organization of the human mitochondrial genome, Nature 290 (1981) 457–465, https://doi.org/10.1038/290457a0.

[10] L.A. Esposito, S. Melov, A. Panov, B.A. Cottrell, D.C. Wallace, Mitochondrial disease in mouse results in increased oxidative stress, Proc. Natl. Acad. Sci. U. S. A. 96 (9) (1999) 4820–4825, https://doi.org/10.1073/pnas.96.9.4820.

[11] V.V. Flis, G. Daum, Lipid transport between the endoplasmic reticulum and mitochondria, Cold Spring Harb. Perspect. Biol. 5 (2013), https://doi.org/10.1101/cshperspect.a013235.

[12] J.M. Berg, J.L. Tymoczko, L. Stryer, Biochemistry, 5th edition, W H Freeman, New York, 2002 Section 18.4, A Proton Gradient Powers the Synthesis of ATP. Available from: https://www.ncbi.nlm.nih.gov/books/NBK22388/.

[13] R. Dhingra, L.A. Kirshenbaum, Succinate dehydrogenase/complex II activity obligatorily links mitochondrial reserve respiratory capacity to cell survival in cardiac myocytes, Cell Death Dis. 6 (2015) e1956, , https://doi.org/10.1038/cddis.2015.310.

[14] C.L. Quinlan, A.L. Orr, I.V. Perevoshchikova, J.R. Treberg, B.A. Ackrell, M.D. Brand, Mitochondrial complex II can generate reactive oxygen species at high rates in both the forward and reverse reactions, J. Biol. Chem. 287 (2012) 27255–27264, https://doi.org/10.1074/jbc.M112.374629.

[15] D.C. Wallace, A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine, Annu. Rev. Genet. 39 (2005) 359–407, https://doi.org/10.1146/annurev.genet.39.110304.095751.

[16] P.H. Reddy, M.F. Beal, Are mitochondria critical in the pathogenesis of Alzheimer's disease? Brain Res. Brain Res. Rev. 49 (2005) 618–632, https://doi.org/10.1016/j.brainresrev.2005.03.004.

[17] P.H. Reddy, M. Manczak, R. Kandimalla, Mitochondria-targeted small molecule SS31: a potential candidate for the treatment of Alzheimer's disease, Hum. Mol. Genet. 26 (2017) 1597, https://doi.org/10.1093/hmg/ddx129.

[18] E.A. Schon, G. Manfredi, Neuronal degeneration and mitochondrial dysfunction, J. Clin. Invest. 111 (2003) 303–312, https://doi.org/10.1172/JCI17741.

[19] P.H. Reddy, X. Yin, M. Manczak, S. Kumar, J.A. Pradeepkiran, M. Vijayan, A.P. Reddy, Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease, Hum. Mol. Genet. 27 (2018) 2502–2516, https://doi.org/10.1093/hmg/ddy154.

[20] M. Manczak, R. Kandimalla, X. Yin, P.H. Reddy, Mitochondrial division inhibitor 1 reduces dynamin-related protein 1 and mitochondrial fission activity, Hum. Mol. Genet. (2018), https://doi.org/10.1093/hmg/ddy335.

[21] R. Kandimalla, M. Manczak, X. Yin, R. Wang, P.H. Reddy, Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease, Hum. Mol. Genet. 27 (2018) 30–40, https://doi.org/10.1093/hmg/ddx381.

[22] M. Manczak, P.H. Reddy, Mitochondrial division inhibitor 1 protects against mutant huntingtin-induced abnormal mitochondrial dynamics and neuronal damage in Huntington's disease, Hum. Mol. Genet. 24 (2015) 7308–7325, https://doi.org/10.1093/hmg/ddv429.

[23] X. Yin, M. Manczak, P.H. Reddy, Mitochondria-targeted molecules MitoQ and SS31 reduce mutant huntingtin-induced mitochondrial toxicity and synaptic damage in Huntington's disease, Hum. Mol. Genet. 25 (2016) 1739–1753, https://doi.org/10.1093/hmg/ddw045.

[24] B. Halliwell, Reactive oxygen species and the central nervous system, J. Neurochem. 59 (1992) 1609–1623, https://doi.org/10.1111/j.1471-4159.1992.tb10990.x.

[25] N. Wiedemann, A.E. Frazier, N. Pfanner, The protein import machinery of mitochondria.J, Biol. Chem. 279 (2004) 14473–14476, https://doi.org/10.1074/jbc.R400003200.

[26] N. Pfanner, A. Geissler, Versatility of the mitochondrial protein import machinery, Nat. Rev. Mol. Cell Biol. 2 (2001) 339–349, https://doi.org/10.1038/35073006.

[27] M.L. Campo, P.M. Peixoto, S. Martínez-Caballero, Revisiting trends on mitochondrial mega-channels for the import of proteins and nucleic acids, J. Bioenerg. Biomembr. 49 (2017) 75–99, https://doi.org/10.1007/s10863-016-9662-z.

[28] B. Mahata, S. Mukherjee, S. Mishra, A. Bandyopadhyay, S. Adhya, Functional delivery of a cytosolic tRNA into mutant mitochondria of human cells, Science 314 (2006) 471–474, https://doi.org/10.1126/science.1129754.

[29] R.C. Scarpulla, Transcriptional paradigms in mammalian mitochondrial biogenesis and function, Physiol. Rev. 88 (2008) 611–638, https://doi.org/10.1152/physrev.00025.2007.

[30] C. Handschin, B.M. Spiegelman, The role of exercise and PGC1α in inflammation and chronic disease, Nature 454 (2008) 463–469, https://doi.org/10.1038/nature07206.

[31] P. Puigserver, B.M. Spiegelman, Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator, Endocr. Rev. 24 (2003) 78–90, https://doi.org/10.1210/er.2002-0012.

[32] J. Lin, C. Handschin, B.M. Spiegelman, Metabolic control through the PGC-1 family of transcription coactivators, Cell Metab. 1 (2005) 361–370, https://doi.org/10.1016/j.cmet.2005.05.004.

[33] H. Zong, J.M. Ren, L.H. Young, M. Pypaert, J. Mu, M.J. Birnbaum, G.I. Shulman, AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 15983–15987, https://doi.org/10.1073/pnas.252625599.

[34] S. Jäger, C. Handschin, J. St-Pierre, B.M. Spiegelman, AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 12017–12022, https://doi.org/10.1073/pnas.0705070104.

[35] N. Lane, Energetics and genetics across the prokaryote-eukaryote divide, Biol. Direct 6 (2011) 35, https://doi.org/10.1186/1745-6150-6-35.

[36] I. Kobayashi, Selfishness and death: raison d'être of restriction, recombination and mitochondria, Trends Genet. 14 (1998) 368–374, https://doi.org/10.1016/S0168-9525(98)01532-7.

[37] Z. Song, M. Ghochani, J.M. McCaffery, T.G. Frey, D.C. Chan, Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion, Mol. Biol. Cell 20 (2009) 3525–3532, https://doi.org/10.1091/mbc.e09-03-0252.

[38] M. Suzuki, A. Neutzner, N. Tjandra, R.J. Youle, Novel structure of the N terminus in yeast Fis1 correlates with a specialized function in mitochondrial fission, J. Biol. Chem. 280 (2005) 21444–21452, https://doi.org/10.1074/jbc.M414092200.

[39] H. Otera, C. Wang, M.M. Cleland, K. Setoguchi, S. Yokota, R.J. Youle, K. Mihara, Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells, J. Cell Biol. 191 (2010) 1141–1158, https://doi.org/10.1083/jcb.201007152.

[40] A.W. Gao, C. Cantó, R.H. Houtkooper, Mitochondrial response to nutrient availability and its role in metabolic disease, EMBO Mol. Med. 6 (2014) 580–589, https://doi.org/10.1002/emmm.201303782.

[41] S. Meeusen, R. DeVay, J. Block, A. Cassidy-Stone, S. Wayson, J.M. McCaffery, J. Nunnari, Mitochondrial inner-membrane fusion and crista maintenance requires the dynamin-related GTPase Mgm1, Cell 127 (2006) 383–395, https://doi.org/10.1016/j.cell.2006.09.021.

[42] C. Delettre, G. Lenaers, J.M. Griffoin, N. Gigarel, C. Lorenzo, P. Belenguer, L. Pelloquin, J. Grosgeorge, C. Turc-Carel, E. Perret, C. Astarie-Dequeker, L. Lasquellec, B. Arnaud, B. Ducommun, J. Kaplan, C.P. Hamel, Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy, Nat. Genet. 26 (2000) 207–210, https://doi.org/10.1038/79936.

[43] C. Alexander, M. Votruba, U.E. Pesch, D.L. Thiselton, S. Mayer, A. Moore, M. Rodriguez, U. Kellner, B. Leo-Kottler, G. Auburger, S.S. Bhattacharya, B. Wissinger, OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28, Nat. Genet. 26 (2000) 211–215, https://doi.org/10.1038/79944.

[44] S. Züchner, I.V. Mersiyanova, M. Muglia, N. Bissar-Tadmouri, J. Rochelle, E.L. Dadali, M. Zappia, E. Nelis, A. Patitucci, J. Senderek, Y. Parman, O. Evgrafov, P.D. Jonghe, Y. Takahashi, S. Tsuji, M.A. Pericak-Vance, A. Quattrone, E. Battaloglu, A.V. Polyakov, V. Timmerman, J.M. Schröder, J.M. Vance, E. Battologlu, Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A, Nat. Genet. 36 (2004) 449–451, https://doi.org/

10.1038/ng1341.
[45] H. Chen, J.M. McCaffery, D.C. Chan, Mitochondrial fusion protects against neurodegeneration in the cerebellum, Cell 130 (2007) 548–562, https://doi.org/10.1016/j.cell.2007.06.026.
[46] H. Chen, A. Chomyn, D.C. Chan, Disruption of fusion results in mitochondrial heterogeneity and dysfunction, J. Biol. Chem. 280 (2005) 26185–26192, https://doi.org/10.1074/jbc.M503062200.
[47] R.A. Gottlieb, D. Bernstein, Mitochondrial remodeling: rearranging, recycling, and reprogramming, Cell Calcium 60 (2016) 88–101, https://doi.org/10.1016/j.ceca.2016.04.006.
[48] A.M. van der Bliek, Q. Shen, S. Kawajiri, Mechanisms of mitochondrial fission and fusion, Cold Spring Harb. Perspect. Biol. 5 (2013), https://doi.org/10.1101/cshperspect.a011072.
[49] A.C. Goldstein, P. Bhatia, J.M. Vento, Mitochondrial disease in childhood: nuclear encoded, Neurotherapeutics 10 (2013) 212–226, https://doi.org/10.1007/s13311-013-0185-6.
[50] N. Ishihara, M. Nomura, A. Jofuku, H. Kato, S.O. Suzuki, K. Masuda, H. Otera, Y. Nakanishi, I. Nonaka, Y.-I. Goto, N. Taguchi, H. Morinaga, M. Maeda, R. Takayanagi, S. Yokota, K. Mihara, Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice, Nat. Cell Biol. 11 (2009) 958–966, https://doi.org/10.1038/ncb1907.
[51] J. Wakabayashi, Z. Zhang, N. Wakabayashi, Y. Tamura, M. Fukaya, T.W. Kensler, M. Iijima, H. Sesaki, The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice, J. Cell Biol. 186 (2009) 805–816, https://doi.org/10.1083/jcb.200903065.
[52] P.M. Rappold, M. Cui, J.C. Grima, R.Z. Fan, K.L. de Mesy-Bentley, L. Chen, X. Zhuang, W.J. Bowers, K. Tieu, Drp1 inhibition attenuates neurotoxicity and dopamine release deficits in vivo, Nat. Commun. 5 (2014) 5244, https://doi.org/10.1038/ncomms6244.
[53] M. Lazarou, D.A. Sliter, L.A. Kane, S.A. Sarraf, C. Wang, J.L. Burman, D.P. Sideris, A.I. Fogel, R.J. Youle, The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy, Nature 524 (2015) 309–314, https://doi.org/10.1038/nature14893.
[54] A.M. Pickrell, R.J. Youle, The roles of PINK1, parkin and mitochondrial fidelity in Parkinson's disease, Neuron 85 (2015) 257, https://doi.org/10.1016/j.neuron.2014.12.007.
[55] B.J. Ryan, S. Hoek, E.A. Fon, R. Wade-Martins, Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease, Trends Biochem. Sci. 40 (2015) 200–210, https://doi.org/10.1016/j.tibs.2015.02.003.
[56] J.T. Greenamyre, T.G. Hastings, Biomedicine. Parkinson's–divergent causes, convergent mechanisms, Science 304 (2004) 1120–1122, https://doi.org/10.1126/science.1098966.
[57] J.J. Lemasters, Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging, Rejuvenation Res. 8 (2005) 3–5, https://doi.org/10.1089/rej.2005.8.3.
[58] R.W. Taylor, D.M. Turnbull, Mitochondrial DNA mutations in human disease, Nat. Rev. Genet. 6 (2005) 389–402, https://doi.org/10.1038/nrg1606.
[59] M. Zeviani, S. Di Donato, Mitochondrial disorders, Brain 127 (2004) 2153–2172, https://doi.org/10.1093/brain/awh259.
[60] E.A. Shoubridge, Nuclear genetic defects of oxidative phosphorylation, Hum. Mol. Genet. 10 (2001) 2277–2284, https://doi.org/10.1093/hmg/10.20.2277.
[61] R. Rossignol, B. Faustin, C. Rocher, M. Malgat, J.-P. Mazat, T. Letellier, Mitochondrial threshold effects, Biochem. J. 370 (2003) 751–762, https://doi.org/10.1042/BJ20021594.
[62] M. Vermulst, J. Wanagat, G.C. Kujoth, J.H. Bielas, P.S. Rabinovitch, T.A. Prolla, L.A. Loeb, DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice, Nat. Genet. 40 (2008) 392–394, https://doi.org/10.1038/ng.95.
[63] J. Müller-Höcker, Cytochrome c oxidase deficient fibres in the limb muscle and diaphragm of man without muscular disease: an age-related alteration, J. Neurol. Sci. 100 (1990) 14–21, https://doi.org/10.1016/0022-510X(90)90006-9.
[64] G. Multhaup, T. Ruppert, A. Schlicksupp, L. Hesse, D. Beher, C.L. Masters, K. Beyreuther, Reactive oxygen species and Alzheimer's disease, Biochem. Pharmacol. 54 (1997) 533–539, https://doi.org/10.1016/S0006-2952(97)00062-2.
[65] Michael Ristow, Kim Zarse, How increased oxidative stress promotes longevity and metabolic health: the concept of mitochondrial hormesis (mitohormesis), Exp. Gerontol. 45 (6) (2010) 410–418, https://doi.org/10.1016/j.exger.2010.03.014.
[66] V.J. Thannickal, B.L. Fanburg, Reactive oxygen species in cell signaling, Am. J. Phys. Lung Cell. Mol. Phys. 279 (2000) L1005–L1028, https://doi.org/10.1152/ajplung.2000.279.6.L1005.
[67] J. Remacle, M. Raes, O. Toussaint, P. Renard, G. Rao, Low levels of reactive oxygen species as modulators of cell function, Mutat. Res. 316 (1995) 103–122.
[68] M. Valko, C.J. Rhodes, J. Moncol, M. Izakovic, M. Mazur, Free radicals, metals and antioxidants in oxidative stress-induced cancer, Chem. Biol. Interact. 160 (2006) 1–40, https://doi.org/10.1016/j.cbi.2005.12.009.
[69] J.K. Andersen, Oxidative stress in neurodegeneration: cause or consequence? Nat. Med. 10 (Suppl) (2004) S18–S25, https://doi.org/10.1038/nrn1434.
[70] V. Calabrese, E. Guagliano, M. Sapienza, M. Panebianco, S. Calafato, E. Puleo, G. Pennisi, C. Mancuso, D.A. Butterfield, A.G. Stella, Redox regulation of cellular stress response in aging and neurodegenerative disorders: role of vitagenes, Neurochem. Res. 32 (2007) 757–773, https://doi.org/10.1007/s11064-006-9203-y.
[71] N.R. Madamanchi, S. Li, C. Patterson, M.S. Runge, Reactive oxygen species regulate heat-shock protein 70 via the JAK/STAT pathway, Arterioscler. Thromb. Vasc. Biol. 21 (2001) 321–326.
[72] R. Kiffin, C. Christian, E. Knecht, A.M. Cuervo, Activation of chaperone-mediated autophagy during oxidative stress, Mol. Biol. Cell 15 (2004) 4829–4840, https://doi.org/10.1091/mbc.e04-06-0477.
[73] N. Breusing, T. Grune, Regulation of proteasome-mediated protein degradation during oxidative stress and aging, Biol. Chem. 389 (2008) 203–209, https://doi.org/10.1515/BC.2008.029.
[74] K. Niforou, C. Cheimonidou, I.P. Trougakos, Molecular chaperones and proteostasis regulation during redox imbalance, Redox Biol. 2 (2014) 323–332, https://doi.org/10.1016/j.redox.2014.01.017.
[75] C.T. Aiken, R.M. Kaake, X. Wang, L. Huang, Oxidative stress-mediated regulation of proteasome complexes, Mol. Cell. Proteomics 10 (2011), https://doi.org/10.1074/mcp.M110.006924.
[76] D. Harman, The biologic clock: the mitochondria? J. Am. Geriatr. Soc. 20 (1972) 145–147, https://doi.org/10.1111/j.1532-5415.1972.tb00787.x.
[77] D. Harman, Aging: a theory based on free radical and radiation chemistry, J. Gerontol. 11 (1956) 298–300, https://doi.org/10.1093/geronj/11.3.298.
[78] B. Lakowski, S. Hekimi, Determination of life-span in Caenorhabditis elegans by four clock genes, Science 272 (1996) 1010–1013.
[79] J. Feng, F. Bussière, S. Hekimi, Mitochondrial electron transport is a key determinant of life span in Caenorhabditis elegans, Dev. Cell 1 (2001) 633–644.
[80] W. Yang, S. Hekimi, Two modes of mitochondrial dysfunction lead independently to lifespan extension in *Caenorhabditis elegans*, Aging Cell 9 (2010) 433–447, https://doi.org/10.1111/j.1474-9726.2010.00571.x.
[81] S.E. Schriner, N.J. Linford, G.M. Martin, P. Treuting, C.E. Ogburn, M. Emond, P.E. Coskun, W. Ladiges, N. Wolf, H. Van Remmen, D.C. Wallace, P.S. Rabinovitch, Extension of murine life span by overexpression of catalase targeted to mitochondria, Science 308 (2005) 1909–1911, https://doi.org/10.1126/science.1106653.
[82] A. Trifunovic, N.-G. Larsson, Mitochondrial dysfunction as a cause of ageing, J. Intern. Med. 263 (2008) 167–178, https://doi.org/10.1111/j.1365-2796.2007.01905.x.
[83] J.M. Van Raamsdonk, S. Hekimi, Deletion of the mitochondrial superoxide dismutase sod-2 extends lifespan in *Caenorhabditis elegans*, PLoS Genet. 5 (2009) e1000361, , https://doi.org/10.1371/journal.pgen.1000361.
[84] Y. Pan, E.A. Schroeder, A. Ocampo, A. Barrientos, G.S. Shadel, Regulation of yeast chronological life span by TORC1 via adaptive mitochondrial ROS signaling, Cell Metab. 13 (2011) 668–678, https://doi.org/10.1016/j.cmet.2011.03.018.
[85] S. Miwa, K. Riyahi, L. Partridge, M.D. Brand, Lack of correlation between mitochondrial reactive oxygen species production and life span in *Drosophila*, Ann. N. Y. Acad. Sci. 1019 (2004) 388–391, https://doi.org/10.1196/annals.1297.069.
[86] M. Ristow, S. Schmeisser, Extending life span by increasing oxidative stress, Free Radic. Biol. Med. 51 (2011) 327–336, https://doi.org/10.1016/j.freeradbiomed.2011.05.010.
[87] G. Fiskum, A.N. Murphy, M.F. Beal, Mitochondria in neurodegeneration: acute ischemia and chronic neurodegenerative diseases, J. Cereb. Blood Flow Metab. 19 (1999) 351–369, https://doi.org/10.1097/00004647-199904000-00001.
[88] R.A. Nakashima, Hexokinase-binding properties of the mitochondrial VDAC protein: inhibition by DCCD and location of putative DCCD-binding sites, J. Bioenerg. Biomembr. 21 (1989) 461–470, https://doi.org/10.1007/BF00762518.
[89] I.G. Onyango, J. Lu, M. Rodova, E. Lezi, A.B. Crafter, R.H. Swerdlow, Regulation of neuron mitochondrial biogenesis and relevance to brain health, Biochim. Biophys. Acta 1802 (2010) 228–234, https://doi.org/10.1016/j.bbadis.2009.07.014.
[90] A. Rasola, P. Bernardi, Mitochondrial permeability transition in Ca(2+)-dependent apoptosis and necrosis, Cell Calcium 50 (2011) 222–233, https://doi.org/10.1016/j.ceca.2011.04.007.
[91] P.H.R. Reddy, T.P. Reddy, Mitochondria as a therapeutic target for aging and neurodegenerative diseases, Curr. Alzheimer Res. (2011), https://doi.org/10.2174/156720511795745401 URL.
[92] P.H. Reddy, Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease, Brain Res. 1415 (2011) 136–148, https://doi.org/10.1016/j.brainres.2011.07.052.
[93] J. Shao, M.I. Diamond, Polyglutamine diseases: emerging concepts in pathogenesis and therapy, Hum. Mol. Genet. 16 (2007) R115–R123, https://doi.org/10.1093/hmg/ddm213 Spec No. 2.
[94] G. Manfredim, M.F. Beal, The role of mitochondria in the pathogenesis of neurodegenerative diseases, Brain Pathol. 10 (2000) 462–472, https://doi.org/10.1111/j.1750-3639.2000.tb00278.x.
[95] Bradley T. Hyman, Creighton H. Phelps, Thomas G. Beach, Eileen H. Bigio, Nigel J. Cairns, Maria C. Carrillo, Dennis W. Dickson, et al., National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease, Alzheimers Dement. 8 (1) (2012) 1–13, https://doi.org/10.1016/j.jalz.2011.10.007.
[96] Jeffrey L. Cummings, Travis Morstorf, Kate Zhong, Alzheimer's disease drug-development pipeline: few candidates, frequent failures, Alzheimers Res. Ther. 6 (4) (2014) 37, https://doi.org/10.1186/alzrt269.
[97] P.H. Reddy, Amyloid precursor protein-mediated free radicals and oxidative damage: implications for the development and progression of Alzheimer's disease, J. Neurochem. 96 (2006) 1–13, https://doi.org/10.1111/j.1471-4159.2005.03530.x.
[98] P.H. Reddy, M.F. Beal, Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease, Trends Mol. Med. 14 (2008) 45–53, https://doi.org/10.1016/j.molmed.2007.12.002.
[99] C.M. Gomes, R. Santos, Neurodegeneration in Friedreich's ataxia: from defective frataxin to oxidative stress, Oxidative Med. Cell. Longev. 2013 (2013) 487534, https://doi.org/10.1155/2013/487534.

[100] X. Wang, W. Wang, L. Li, G. Perry, H. Lee, X. Zhu, Oxidative stress and mitochondrial dysfunction in Alzheimer's disease, Biochim. Biophys. Acta 1842 (2014) 1240–1247, https://doi.org/10.1016/j.bbadis.2013.10.015.
[101] P. Bubber, V. Haroutunian, G. Fisch, J.P. Blass, G.E. Gibson, Mitochondrial abnormalities in Alzheimer brain: mechanistic implications, Ann. Neurol. 57 (2005) 695–703, https://doi.org/10.1002/ana.20474.
[102] S. Sekar, J. McDonald, L. Cuyugan, J. Aldrich, A. Kurdoglu, J. Adkins, G. Serrano, T.G. Beach, D.W. Craig, J. Valla, E.M. Reiman, W.S. Liang, Alzheimer's disease is associated with altered expression of genes involved in immune response and mitochondrial processes in astrocytes, Neurobiol. Aging 36 (2015) 583–591, https://doi.org/10.1016/j.neurobiolaging.2014.09.027.
[103] E.A. Schon, E. Area-Gomez, Mitochondria-associated ER membranes in Alzheimer disease, Mol. Cell. Neurosci. 55 (2013) 26–36, https://doi.org/10.1016/j.mcn.2012.07.011.
[104] S. Varadarajan, S. Yatin, M. Aksenova, D.A. Butterfield, Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity, J. Struct. Biol. 130 (2000) 184–208, https://doi.org/10.1006/jsbi.2000.4274.
[105] M.F. Beal, Mitochondrial dysfunction in neurodegenerative diseases, Biochim. Biophys. Acta 1366 (1998) 211–223, https://doi.org/10.1016/S0005-2728(98)00114-5.
[106] T. Pringsheim, N. Jette, A. Frolkis, T.D.L. Steeves, The prevalence of Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 29 (2014) 1583–1590, https://doi.org/10.1002/mds.25945.
[107] A. Elbaz, L. Carcaillon, S. Kab, F. Moisan, Epidemiology of Parkinson's disease, Revue Neurologique, Neuroepidemiology 172 (2016) 14–26, https://doi.org/10.1016/j.neurol.2015.09.012.
[108] A. Smilansky, L. Dangoor, I. Nakdimon, D. Ben-Hail, D. Mizrachi, V. Shoshan-Barmatz, The voltage-dependent anion channel 1 mediates amyloid β toxicity and represents a potential target for Alzheimer disease therapy, J. Biol. Chem. 290 (2015) 30,670–30,683, https://doi.org/10.1074/jbc.M115.691493.
[109] J. Blesa, I. Trigo-Damas, A. Quiroga-Varela, V.R. Jackson-Lewis, Oxidative stress and Parkinson's disease, Front. Neuroanat. 9 (2015), https://doi.org/10.3389/fnana.2015.00091.
[110] T.R. Mhyre, J.T. Boyd, R.W. Hamill, K.A. Maguire-Zeiss, Parkinson's disease, Subcell. Biochem. 65 (2012) 389–455, https://doi.org/10.1007/978-94-007-5416-4_16.
[111] J.W. Langston, P. Ballard, J.W. Tetrud, I. Irwin, Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis, Science 219 (1983) 979–980, https://doi.org/10.1126/science.6823561.
[112] M.E. Johnson, L. Bobrovskaya, An update on the rotenone models of Parkinson's disease: their ability to reproduce the features of clinical disease and model gene-environment interactions, Neurotoxicology 46 (2015) 101–116, https://doi.org/10.1016/j.neuro.2014.12.002.
[113] Y. Luo, A. Hoffer, B. Hoffer, X. Qi, Mitochondria: a therapeutic target for Parkinson's disease? Int. J. Mol. Sci. 16 (2015) 20,704–20,730, https://doi.org/10.3390/ijms160920704.
[114] P. Luoma, A. Melberg, J.O. Rinne, J.A. Kaukonen, N.N. Nupponen, R.M. Chalmers, A. Oldfors, I. Rautakorpi, L. Peltonen, K. Majamaa, H. Somer, A. Suomalainen, Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study, Lancet 364 (2004) 875–882, https://doi.org/10.1016/S0140-6736(04)16983-3.
[115] P.M. Keeney, C.K. Quigley, L.D. Dunham, C.M. Papageorge, S. Iyer, R.R. Thomas, K.M. Schwarz, P.A. Trimmer, S.M. Khan, F.R. Portell, K.E. Bergquist, J.P. Bennett, Mitochondrial gene therapy augments mitochondrial physiology in a Parkinson's disease cell model, Hum. Gene Ther. 20 (2009) 897–907, https://doi.org/10.1089/hum.2009.023.
[116] R.T. Matthews, R.J. Ferrante, P. Klivenyi, L. Yang, A.M. Klein, G. Mueller, R. Kaddurah- Daouk, M.F. Beal, Creatine and cyclocreatine attenuate MPTP neurotoxicity, Exp. Neurol. 157 (1999) 142–149, https://doi.org/10.1006/exnr.1999.7049.
[117] M.D. Rawlins, N.S. Wexler, A.R. Wexler, S.J. Tabrizi, I. Douglas, S.J.W. Evans, L. Smeeth, The prevalence of huntington's disease, Neuroepidemiology 46 (2016) 144–153, https://doi.org/10.1159/000443738.
[118] M. Muller, B.R. Leavitt, Iron dysregulation in Huntington's disease, J. Neurochem. 130 (2014) 328–350, https://doi.org/10.1111/jnc.12739.
[119] M.W. Brazier, A.G. Wedd, S.J. Collins, Antioxidant and metal chelation-based therapies in the treatment of prion disease, Antioxidants (Basel) 3 (2014) 288–308, https://doi.org/10.3390/antiox3020288.
[120] H.D. Rosas, Y.I. Chen, G. Doros, D.H. Salat, N. Chen, K.K. Kwong, A. Bush, J. Fox, S.M. Hersch, Alterations in brain transition metals in Huntington disease: an evolving and intricate story, Arch. Neurol. 69 (2012) 887–893, https://doi.org/10.1001/archneurol.2011.2945.
[121] M.T. Heneka, G.E. Landreth, M. Hüll, Drug insight: effects mediated by peroxisome proliferator-activated receptor-gamma in CNS disorders, Nat. Clin. Pract. Neurol. 3 (2007) 496–504, https://doi.org/10.1038/ncpneuro0586.
[122] P.H. Reddy, P. Mao, M. Manczak, Mitochondrial structural and functional dynamics in Huntington's disease, Brain Res. Rev. 61 (2009) 33–48, https://doi.org/10.1016/j.brainresrev.2009.04.001.
[123] P.H. Reddy, M. Williams, V. Charles, L. Garrett, L. Pike-Buchanan, W.O. Whetsell, G. Miller, D.A. Tagle, Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full-length HD cDNA, Nat. Genet. 20 (1998) 198–202, https://doi.org/10.1038/2510.
[124] F.O. Walker, Huntington's disease, Lancet 369 (2007) 218–228, https://doi.org/10.1016/S0140-6736(07)60111-1.
[125] R.A. Quintanilla, Y.N. Jin, R. von Bernhardi, G.V.W. Johnson, Mitochondrial permeability transition pore induces mitochondria injury in Huntington disease, Mol. Neurodegener. 8 (2013) 45, https://doi.org/10.1186/1750-1326-8-45.
[126] J.J. Shacka, K.A. Roth, Bcl-2 family and the central nervous system: from rheostat to real complex, Cell Death Differ. 13 (2006) 1299–1304, https://doi.org/10.1038/sj.cdd.4401974.
[127] L. Cui, H. Jeong, F. Borovecki, C.N. Parkhurst, N. Tanese, D. Krainc, Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration, Cell 127 (2006) 59–69, https://doi.org/10.1016/j.cell.2006.09.015.
[128] E.O. Talbott, A.M. Malek, D. Lacomis, Chapter 13 - the epidemiology of amyotrophic lateral sclerosis, in: M.J. Aminoff, F. Boller, D.F. Swaab (Eds.), Handbook of Clinical Neurology, Neuroepidemiology, Elsevier, 2016, pp. 225–238, , https://doi.org/10.1016/B978-0-12-802973-2.00013-6.
[129] E. Pollari, G. Goldsteins, G. Bart, J. Koistinaho, R. Giniatullin, The role of oxidative stress in degeneration of the neuromuscular junction in amyotrophic lateral sclerosis, Front. Cell. Neurosci. 8 (2014), https://doi.org/10.3389/fncel.2014.00131.
[130] R.A. Quintanilla, Y.N. Jin, K. Fuenzalida, M. Bronfman, G.V.W. Johnson, Rosiglitazone treatment prevents mitochondrial dysfunction in mutant huntingtin-expressing cells: possible role of peroxisome proliferator-activated receptor-gamma (PPARgamma) in the pathogenesis of Huntington disease, J. Biol. Chem. 283 (2008) 25628–25637, https://doi.org/10.1074/jbc.M804291200.
[131] W. Tan, P. Pasinelli, D. Trotti, Role of mitochondria in mutant SOD1 linked amyotrophic lateral sclerosis, Biochim. Biophys. Acta 1842 (2014) 1295–1301, https://doi.org/10.1016/j.bbadis.2014.02.009.
[132] A.P. Russell, S. Wada, L. Vergani, M.B. Hock, S. Lamon, B. Léger, T. Ushida, R. Cartoni, G.D. Wadley, P. Hespel, A. Kralli, G. Soraru, C. Angelini, T. Akimoto, Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis, Neurobiol. Dis. 49 (2013) 107–117, https://doi.org/10.1016/j.nbd.2012.08.015.
[133] M. Kiaei, Peroxisome proliferator-activated receptor-gamma in amyotrophic lateral sclerosis and Huntington's disease, PPAR Res. 2008 (2008) 418,765, https://doi.org/10.1155/2008/418765.
[134] J. Magrané, G. Manfredi, Mitochondrial function, morphology, and axonal transport in amyotrophic lateral sclerosis, Antioxid. Redox Signal. 11 (2009) 1615–1626, https://doi.org/10.1089/ars.2009.2604.
[135] N.D. Perera, R.K. Sheean, J.W. Scott, B.E. Kemp, M.K. Horne, B.J. Turner, Mutant TDP-43 deregulates AMPK activation by PP2A in ALS models, PLoS ONE 9 (2014) e90449, , https://doi.org/10.1371/journal.pone.0090449.
[136] D. Kim, M.D. Nguyen, M.M. Dobbin, A. Fischer, F. Sananbenesi, J.T. Rodgers, I. Delalle, J.A. Baur, G. Sui, S.M. Armour, P. Puigserver, D.A. Sinclair, L.-H. Tsai, SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis, EMBO J. 26 (2007) 3169–3179, https://doi.org/10.1038/sj.emboj.7601758.
[137] E. Barbieri, D. Agostini, E. Polidori, L. Potenza, M. Guescini, F. Lucertini, G. Annibalini, L. Stocchi, M. De Santi, V. Stocchi, The pleiotropic effect of physical exercise on mitochondrial dynamics in aging skeletal muscle [WWW Document], Oxidative Med. Cell. Longev. (2015), https://doi.org/10.1155/2015/917085.
[138] S.K. POWERS, M.J. JACKSON, Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production, Physiol. Rev. 88 (2008) 1243–1276, https://doi.org/10.1152/physrev.00031.2007.
[139] V. Benedusi, F. Martorana, L. Brambilla, A. Maggi, D. Rossi, The peroxisome proliferator-activated receptor γ (PPARγ) controls natural protective mechanisms against lipid peroxidation in amyotrophic lateral sclerosis, J. Biol. Chem. 287 (2012) 35899–35911, https://doi.org/10.1074/jbc.M112.366419.
[140] T. Wenz, F. Diaz, D. Hernandez, C.T. Moraes, Endurance exercise is protective for mice with mitochondrial myopathy, J. Appl. Physiol. 106 (2009) 1712–1719, https://doi.org/10.1152/japplphysiol.91571.2008.
[141] E.V. Menshikova, V.B. Ritov, L. Fairfull, R.E. Ferrell, D.E. Kelley, B.H. Goodpaster, Effects of exercise on mitochondrial content and function in aging human skeletal muscle, J. Gerontol. A Biol. Sci. Med. Sci. 61 (2006) 534–540.
[142] E. Wesselink, W.A.C. Koekkoek, S. Grefte, R.F. Witkamp, A.R.H. van Zanten, Feeding mitochondria: potential role of nutritional components to improve critical illness convalescence, Clin. Nutr. (2018), https://doi.org/10.1016/j.clnu.2018.08.032.
[143] E.J. Masoro, Overview of caloric restriction and ageing, Mechanisms of Ageing and Development, Dietary Restriction, Longevity and Ageing - The Current State of Our Knowledge and Ignorance, 126 2005, pp. 913–922, , https://doi.org/10.1016/j.mad.2005.03.012.
[144] A.J. Kowaltowski, Caloric restriction and redox state: does this diet increase or decrease oxidant production? Redox Rep. 16 (2011) 237–241, https://doi.org/10.1179/1351000211Y.0000000014.
[145] T. Hsieh, X. Lu, Z. Wang, J.M. Wu, Induction of quinone reductase NQO1 by resveratrol in human K562 cells involves the antioxidant response element ARE and is accompanied by nuclear translocation of transcription factor Nrf2, Med. Chem. 2 (2006) 275–285, https://doi.org/10.2174/157340606776930709.
[146] Z. Ungvari, C. Parrado-Fernandez, A. Csiszar, R. de Cabo, Mechanisms underlying caloric restriction and life span regulation: implications for vascular aging, Circ. Res. 102 (2008) 519–528, https://doi.org/10.1161/CIRCRESAHA.107.168369.
[147] S. Ahola-Erkkilä, C.J. Carroll, K. Peltola-Mjösund, V. Tulkki, I. Mattila, T. Seppänen-Laakso, M. Oresic, H. Tyynismaa, A. Suomalainen, Ketogenic diet slows down mitochondrial myopathy progression in mice, Hum. Mol. Genet. 19 (2010) 1974–1984, https://doi.org/10.1093/hmg/ddq076.
[148] S.A. Masino, J.D. Geiger, Are purines mediators of the anticonvulsant/neuroprotective effects of ketogenic diets? Trends Neurosci. 31 (2008) 273–278, https://doi.org/10.1016/j.tins.2008.02.009.
[149] C.C. Danta, P. Piplani, The discovery and development of new potential

antioxidant agents for the treatment of neurodegenerative diseases, Expert Opin. Drug Discovery 9 (2014) 1205–1222, https://doi.org/10.1517/17460441.2014.942218.
[150] J.M. Forbes, D.R. Thorburn, Mitochondrial dysfunction in diabetic kidney disease, Nat. Rev. Nephrol. 14 (2018) 291–312, https://doi.org/10.1038/nrneph.2018.9.
[151] H.H. Szeto, A.V. Birk, Serendipity and the discovery of novel compounds that restore mitochondrial plasticity, Clin. Pharmacol. Ther. 96 (2014) 672–683, https://doi.org/10.1038/clpt.2014.174.
[152] H.H. Szeto, First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics, Br. J. Pharmacol. 171 (2014) 2029–2050, https://doi.org/10.1111/bph.12461.
[153] S. Moussaoui, M.C. Obinu, N. Daniel, M. Reibaud, V. Blanchard, A. Imperato, The antioxidant ebselen prevents neurotoxicity and clinical symptoms in a primate model of Parkinson's disease, Exp. Neurol. 166 (2000) 235–245, https://doi.org/10.1006/exnr.2000.7516.
[154] T.L. Horvath, S. Diano, C. Leranth, L.M. Garcia-Segura, M.A. Cowley, M. Shanabrough, J.D. Elsworth, P. Sotonyi, R.H. Roth, E.H. Dietrich, R.T. Matthews, C.J. Barnstable, D.E. Redmond, Coenzyme Q induces nigral mitochondrial uncoupling and prevents dopamine cell loss in a primate model of Parkinson's disease, Endocrinology 144 (2003) 2757–2760, https://doi.org/10.1210/en.2003-0163.
[155] Y. Levites, O. Weinreb, G. Maor, M.B.H. Youdim, S. Mandel, Green tea polyphenol (–)-epigallocatechin-3-gallate prevents *N*-methyl-4-phenyl-1,2,3,6 tetrahydropyridine- induced dopaminergic neurodegeneration, J. Neurochem. 78 (2001) 1073–1082, https://doi.org/10.1046/j.1471-4159.2001.00490.x.
[156] S. Karunakaran, L. Diwakar, U. Saeed, V. Agarwal, S. Ramakrishnan, S. Iyengar, V. Ravindranath, Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by alpha-lipoic acid, FASEB J. 21 (2007) 2226–2236, https://doi.org/10.1096/fj.06-7580com.
[157] C. Karaaslan, S. Suzen, Antioxidant properties of melatonin and its potential action in diseases, Curr. Top. Med. Chem. 15 (2015) 894–903, https://doi.org/10.2174/1568026615666150220120946.
[158] M.R. Ramis, S. Esteban, A. Miralles, D.-X. Tan, R.J. Reiter, Protective effects of melatonin and mitochondria-targeted antioxidants against oxidative stress: a review, Curr. Med. Chem. 22 (2015) 2690–2711.
[159] D.P. Cardinali, E.S. Pagano, P.A. Scacchi Bernasconi, R. Reynoso, P. Scacchi, Melatonin and mitochondrial dysfunction in the central nervous system, Horm. Behav. 63 (2013) 322–330, https://doi.org/10.1016/j.yhbeh.2012.02.020.
[160] H.J. Kwon, M.-Y. Cha, D. Kim, D.K. Kim, M. Soh, K. Shin, T. Hyeon, I. Mook-Jung, Mitochondria-targeting ceria nanoparticles as antioxidants for Alzheimer's disease, ACS Nano 10 (2016) 2860–2870, https://doi.org/10.1021/acsnano.5b08045.
[161] M.P. Murphy, R.A.J. Smith, Targeting antioxidants to mitochondria by conjugation to lipophilic cations, Annu. Rev. Pharmacol. Toxicol. 47 (2007) 629–656, https://doi.org/10.1146/annurev.pharmtox.47.120505.105110.
[162] J. McLachlan, E. Beattie, M.P. Murphy, C.H.H. Koh-Tan, E. Olson, W. Beattie, A.F. Dominiczak, S.A. Nicklin, D. Graham, Combined therapeutic benefit of mitochondria- targeted antioxidant, MitoQ10, and angiotensin receptor blocker, losartan, on cardiovascular function, J. Hypertens. 32 (2014) 555–564, https://doi.org/10.1097/HJH.0000000000000054.
[163] J.R. Mercer, E. Yu, N. Figg, K.-K. Cheng, T.A. Prime, J.L. Griffin, M. Masoodi, A. Vidal- Puig, M.P. Murphy, M.R. Bennett, The mitochondria-targeted antioxidant MitoQ decreases features of the metabolic syndrome in ATM+/-/ApoE-/- mice, Free Radic. Biol. Med. 52 (2012) 841–849, https://doi.org/10.1016/j.freeradbiomed.2011.11.026.
[164] R.A.J. Smith, M.P. Murphy, Animal and human studies with the mitochondria-targeted antioxidant MitoQ, Ann. N. Y. Acad. Sci. 1201 (2010) 96–103, https://doi.org/10.1111/j.1749-6632.2010.05627.x.
[165] M.S. Ward, N.B. Flemming, L.A. Gallo, A.K. Fotheringham, D.A. McCarthy, A. Zhuang, P.H. Tang, D.J. Borg, H. Shaw, B. Harvie, D.R. Briskey, L.A. Roberts, M.R. Plan, M.P. Murphy, M.P. Hodson, J.M. Forbes, Targeted mitochondrial therapy using MitoQ shows equivalent renoprotection to angiotensin converting enzyme inhibition but no combined synergy in diabetes, Sci. Rep. 7 (2017) 15190, https://doi.org/10.1038/s41598-017-15589-x.
[166] D.A. Lowes, B.M.V. Thottakam, N.R. Webster, M.P. Murphy, H.F. Galley, The mitochondria-targeted antioxidant MitoQ protects against organ damage in a lipopolysaccharide-peptidoglycan model of sepsis, Free Radic. Biol. Med. 45 (2008) 1559–1565, https://doi.org/10.1016/j.freeradbiomed.2008.09.003.
[167] Y. Moon, K.H. Lee, J.-H. Park, D. Geum, K. Kim, Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: protective effect of coenzyme Q10, J. Neurochem. 93 (2005) 1199–1208, https://doi.org/10.1111/j.1471-4159.2005.03112.x.
[168] J.S. Yun, H.K. Na, K.-S. Park, Y.H. Lee, E.Y. Kim, S.Y. Lee, J.-I. Kim, J.-H. Kang, D.S. Kim, K.H. Choi, Protective effects of Vitamin E on endocrine disruptors, PCB-induced dopaminergic neurotoxicity, Toxicology 216 (2005) 140–146, https://doi.org/10.1016/j.tox.2005.08.017.
[169] S. Fahn, A pilot trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's disease, Ann. Neurol. 32 (Suppl) (1992) S128–S132.
[170] S.M. Zhang, M.A. Hernán, H. Chen, D. Spiegelman, W.C. Willett, A. Ascherio, Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk, Neurology 59 (2002) 1161–1169, https://doi.org/10.1212/01.WNL.0000028688.75881.12.
[171] Z. Wu, P. Puigserver, U. Andersson, C. Zhang, G. Adelmant, V. Mootha, A. Troy, S. Cinti, B. Lowell, R.C. Scarpulla, B.M. Spiegelman, Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1, Cell 98 (1999) 115–124, https://doi.org/10.1016/S0092-8674(00)80611-X.
[172] C. Viscomi, E. Bottani, G. Civiletto, R. Cerutti, M. Moggio, G. Fagiolari, E.A. Schon, C. Lamperti, M. Zeviani, In vivo correction of COX deficiency by activation of the AMPK/PGC-1α axis, Cell Metab. 14 (2011) 80–90, https://doi.org/10.1016/j.cmet.2011.04.011.
[173] J.K. McGill, M.F. Beal, PGC-1alpha, a new therapeutic target in Huntington's disease? Cell 127 (2006) 465–468, https://doi.org/10.1016/j.cell.2006.10.023.
[174] J.C. Corona, M.R. Duchen, PPARγ and PGC-1α as therapeutic targets in Parkinson's, Neurochem. Res. 40 (2015) 308–316, https://doi.org/10.1007/s11064-014-1377-0.
[175] K. Róna-Vörös, P. Weydt, The role of PGC-1α in the pathogenesis of neurodegenerative disorders, Curr. Drug Targets 11 (2010) 1262–1269, https://doi.org/10.2174/138945011007011262v.
[176] O. Ozden, S.-H. Park, H.-S. Kim, H. Jiang, M.C. Coleman, D.R. Spitz, D. Gius, Acetylation of MnSOD directs enzymatic activity responding to cellular nutrient status or oxidative stress, Aging (Albany NY) 3 (2011) 102–107, https://doi.org/10.18632/aging.100291.
[177] G. Sweeney, J. Song, The association between PGC-1α and Alzheimer's disease, Anat. Cell Biol. 49 (2016) 1–6, https://doi.org/10.5115/acb.2016.49.1.1.
[178] J.G. Wood, B. Rogina, S. Lavu, K. Howitz, S.L. Helfand, M. Tatar, D. Sinclair, Sirtuin activators mimic caloric restriction and delay ageing in metazoans, Nature 430 (2004) 686–689, https://doi.org/10.1038/nature02789.
[179] D. Beher, J. Wu, S. Cumine, K.W. Kim, S.-C. Lu, L. Atangan, M. Wang, Resveratrol is not a direct activator of SIRT1 enzyme activity, Chem. Biol. Drug Des. 74 (2009) 619–624, https://doi.org/10.1111/j.1747-0285.2009.00901.x.
[180] C. Cantó, Z. Gerhart-Hines, J.N. Feige, M. Lagouge, L. Noriega, J.C. Milne, P.J. Elliott, P. Puigserver, J. Auwerx, AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity, Nature 458 (2009) 1056–1060, https://doi.org/10.1038/nature07813.
[181] J.A. Baur, K.J. Pearson, N.L. Price, H.A. Jamieson, C. Lerin, A. Kalra, V.V. Prabhu, J.S. Allard, G. Lopez-Lluch, K. Lewis, P.J. Pistell, S. Poosala, K.G. Becker, O. Boss, D. Gwinn, M. Wang, S. Ramaswamy, K.W. Fishbein, R.G. Spencer, E.G. Lakatta, D. Le Couteur, R.J. Shaw, P. Navas, P. Puigserver, D.K. Ingram, R. de Cabo, D.A. Sinclair, Resveratrol improves health and survival of mice on a high-calorie diet, Nature 444 (2006) 337–342, https://doi.org/10.1038/nature05354.
[182] A.Z. Herskovits, L. Guarente, SIRT1 in neurodevelopment and brain senescence, Neuron 81 (2014) 471–483, https://doi.org/10.1016/j.neuron.2014.01.028.
[183] G.G. Kuiper, J.G. Lemmen, B. Carlsson, J.C. Corton, S.H. Safe, P.T. van der Saag, B. van der Burg, J.A. Gustafsson, Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta, Endocrinology 139 (1998) 4252–4263, https://doi.org/10.1210/endo.139.10.6216.
[184] S.-Z. Xu, W. Zhong, M. Ghavideldarestani, R. Saurabh, S.W. Lindow, S.L. Atkin, Multiple mechanisms of soy isoflavones against oxidative stress-induced endothelium injury, Free Radic. Biol. Med. 47 (2009) 167–175, https://doi.org/10.1016/j.freeradbiomed.2009.04.021.
[185] K.A. Rasbach, R.G. Schnellmann, Isoflavones promote mitochondrial biogenesis, J. Pharmacol. Exp. Ther. 325 (2008) 536–543, https://doi.org/10.1124/jpet.107.134882.
[186] M.R. de Oliveira, S.M. Nabavi, N. Braidy, W.N. Setzer, T. Ahmed, S.F. Nabavi, Quercetin and the mitochondria: a mechanistic view, Biotechnol. Adv. 34 (2016) 532–549, https://doi.org/10.1016/j.biotechadv.2015.12.014.
[187] D.C. Nieman, A.S. Williams, R.A. Shanely, F. Jin, S.R. Mcanulty, N.T. Triplett, M.D. Austin, D.A. Henson, Quercetin's influence on exercise performance and muscle mitochondrial biogenesis, Med. Sci. Sports Exerc. 42 (2010) 338–345, https://doi.org/10.1249/mss.0b013e3181b18fa3.
[188] Y.-X. Wang, PPARs: diverse regulators in energy metabolism and metabolic diseases, Cell Res. 20 (2010) 124, https://doi.org/10.1038/cr.2010.13.
[189] T. Wenz, F. Diaz, B.M. Spiegelman, C.T. Moraes, Activation of the PPAR/PGC-1alpha pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype, Cell Metab. 8 (2008) 249–256, https://doi.org/10.1016/j.cmet.2008.07.006.
[190] A. Trifunovic, A. Wredenberg, M. Falkenberg, J.N. Spelbrink, A.T. Rovio, C.E. Bruder, M. Bohlooly-Y, S. Gidlöf, A. Oldfors, R. Wibom, J. Törnell, H.T. Jacobs, N.-G. Larsson, Premature ageing in mice expressing defective mitochondrial DNA polymerase, Nature 429 (2004) 417–423, https://doi.org/10.1038/nature02517.
[191] J.C. Komen, D.R. Thorburn, Turn up the power – pharmacological activation of mitochondrial biogenesis in mouse models, Br. J. Pharmacol. 171 (2014) 1818–1836, https://doi.org/10.1111/bph.12413.
[192] R.N. Lightowlers, Z.M. Chrzanowska-Lightowlers, Salvaging hope: is increasing NAD^+ a key to treating mitochondrial myopathy? EMBO Mol. Med. 6 (2014) 705–707, https://doi.org/10.15252/emmm.201404179.
[193] H. Chen, D.C. Chan, Mitochondrial dynamics–fusion, fission, movement, and mitophagy–in neurodegenerative diseases, Hum. Mol. Genet. 18 (2009) R169–R176, https://doi.org/10.1093/hmg/ddp326.
[194] N.D. Georgakopoulos, G. Wells, M. Campanella, The pharmacological regulation of cellular mitophagy, Nat. Chem. Biol. 13 (2017) 136–146, https://doi.org/10.1038/nchembio.2287.
[195] G.F.G. Allen, R. Toth, J. James, I.G. Ganley, Loss of iron triggers PINK1/Parkin-independent mitophagy, EMBO Rep. 14 (2013) 1127–1135, https://doi.org/10.1038/embor.2013.168.
[196] H.B. Suliman, C.A. Piantadosi, Mitochondrial quality control as a therapeutic target, Pharmacol. Rev. 68 (2016) 20–48, https://doi.org/10.1124/pr.115.011502.
[197] A. Cassidy-Stone, J.E. Chipuk, E. Ingerman, C. Song, C. Yoo, T. Kuwana, M.J. Kurth, J.T. Shaw, J.E. Hinshaw, D.R. Green, J. Nunnari, Chemical inhibition of the mitochondrial division dynamin reveals its role in Bax/Bak-dependent

mitochondrial outer membrane permeabilization, Dev. Cell 14 (2008) 193–204, https://doi.org/10.1016/j.devcel.2007.11.019.
[198] E. Macia, M. Ehrlich, R. Massol, E. Boucrot, C. Brunner, T. Kirchhausen, Dynasore, a cell-permeable inhibitor of dynamin, Dev. Cell 10 (2006) 839–850, https://doi.org/10.1016/j.devcel.2006.04.002.
[199] X. Qi, N. Qvit, Y.-C. Su, D. Mochly-Rosen, A novel Drp1 inhibitor diminishes aberrant mitochondrial fission and neurotoxicity, J. Cell Sci. 126 (2013) 789–802, https://doi.org/10.1242/jcs.114439.
[200] R.R. Thomas, S.M. Khan, R.M. Smigrodzki, I.G. Onyango, J. Dennis, O.M. Khan, F.R. Portell, J.P. Bennett, RhTFAM treatment stimulates mitochondrial oxidative metabolism and improves memory in aged mice, Aging (Albany NY) 4 (2012) 620–635.
[201] Y. Suzuki, Exploring transduction mechanisms of protein transduction domains (PTDs) in living cells utilizing single-quantum dot tracking (SQT) technology, Sensors (Basel) 12 (2012) 549–572, https://doi.org/10.3390/s120100549.
[202] V. Weissig, G.G. D'Souza, V.P. Torchilin, DQAsome/DNA complexes release DNA upon contact with isolated mouse liver mitochondria, J. Control. Release 75 (2001) 401–408, https://doi.org/10.1016/S0168-3659(01)00392-3.
[203] Y. Yasuzaki, Y. Yamada, H. Harashima, Mitochondrial matrix delivery using MITO- Porter, a liposome-based carrier that specifies fusion with mitochondrial membranes, Biochem. Biophys. Res. Commun. 397 (2010) 181–186, https://doi.org/10.1016/j.bbrc.2010.05.070.
[204] M. Lee, J.S. Choi, M.J. Choi, Y.K. Pak, B.D. Rhee, K.S. Ko, DNA delivery to the mitochondria sites using mitochondrial leader peptide conjugated poly-ethylenimine, J. Drug Target. 15 (2007) 115–122, https://doi.org/10.1080/10611860600953555.
[205] R.W. Taylor, P.F. Chinnery, D.M. Turnbull, R.N. Lightowlers, In-vitro genetic modification of mitochondrial function, Hum. Reprod. 15 (Suppl. 2) (2000) 79–85.
[206] P.F. Chinnery, R.W. Taylor, K. Diekert, R. Lill, D.M. Turnbull, R.N. Lightowlers, Peptide nucleic acid delivery to human mitochondria, Gene Ther. 6 (1999) 1919–1928, https://doi.org/10.1038/sj.gt.3301061.
[207] J.M. Gott, G.M. Naegele, S.J. Howell, Electroporation of DNA into physarum polycephalum mitochondria: effects on transcription and RNA editing in isolated organelles, Genes (Basel) (2016) 7, https://doi.org/10.3390/genes7120128.
[208] T. Klopstock, B. Klopstock, H. Prokisch, Mitochondrial replacement approaches: challenges for clinical implementation, Genome Med. 8 (2016) 126, https://doi.org/10.1186/s13073-016-0380-2.
[209] D.P. Wolf, N. Mitalipov, S. Mitalipov, Mitochondrial replacement therapy in reproductive medicine, Trends Mol. Med. 21 (2015) 68–76, https://doi.org/10.1016/j.molmed.2014.12.001.
[210] A.J. Tanaka, M.V. Sauer, D. Egli, D.H. Kort, Harnessing the stem cell potential: the path to prevent mitochondrial disease, Nat. Med. 19 (2013) 1578–1579, https://doi.org/10.1038/nm.3422.