CNS Neuroscience & Therapeutics

REVIEW

Mitochondrial Dysfunction and Biogenesis in Neurodegenerative diseases: Pathogenesis and Treatment

Mojtaba Golpich,[1] Elham Amini,[1] Zahurin Mohamed,[2] Raymond Azman Ali,[1] Norlinah Mohamed Ibrahim[1] & Abolhassan Ahmadiani[3]

1 Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, Kuala Lumpur, Malaysia
2 Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
3 Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Keywords
Mitochondrial Biogenesis; Mitochondrial complexes; Mitochondrial Dysfunction; Neurodegenerative Diseases; Pathogenesis; Treatment.

Correspondence
A. Ahmadiani, Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Daneshjoo Blvd, Evin Ave, P.O. Box: 19615-1178, Tehran 1983963113, Iran.
Tel.: +9821-22429765-9;
Fax: +9821-22431624 & +9821-22432047;
E-mail: aahmadiani@yahoo.com
and
N. Mohamed Ibrahim, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, 56000 Kuala Lumpur, Malaysia.
Tel.: +603-91456074;
Fax: +603-91456640;
E-mail: norlinah@ppukm.ukm.my
Received 2 July 2016; revision 29 September 2016; accepted 4 October 2016

doi: 10.1111/cns.12655

The first two authors contributed equally to this work.

SUMMARY

Neurodegenerative diseases are a heterogeneous group of disorders that are incurable and characterized by the progressive degeneration of the function and structure of the central nervous system (CNS) for reasons that are not yet understood. Neurodegeneration is the umbrella term for the progressive death of nerve cells and loss of brain tissue. Because of their high energy requirements, neurons are especially vulnerable to injury and death from dysfunctional mitochondria. Widespread damage to mitochondria causes cells to die because they can no longer produce enough energy. Several lines of pathological and physiological evidence reveal that impaired mitochondrial function and dynamics play crucial roles in aging and pathogenesis of neurodegenerative diseases. As mitochondria are the major intracellular organelles that regulate both cell survival and death, they are highly considered as a potential target for pharmacological-based therapies. The purpose of this review was to present the current status of our knowledge and understanding of the involvement of mitochondrial dysfunction in pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) and the importance of mitochondrial biogenesis as a potential novel therapeutic target for their treatment. Likewise, we highlight a concise overview of the key roles of mitochondrial electron transport chain (ETC.) complexes as well as mitochondrial biogenesis regulators regarding those diseases.

Introduction

Mitochondria play important roles in cell respiratory processes, metabolism, energy production, intracellular signaling, free radical production, and apoptosis [1,2]. These super dynamic organelles can change their morphology, number and function in reaction to physiological situations, and stressors like hormones, diet, temperature, and exercise [2]. Many lines of evidence suggest that mitochondria can critically regulate cell death and survival, play an essential role in aging, and are one of the key features of neurodegeneration [3]. In the central nervous system (CNS), sufficient energy supply which required for neuronal survival and excitability is mostly dependent on mitochondrial sources; therefore, brain is much more vulnerable to mitochondrial dysfunction [4]. Appropriate function of mitochondria is fundamental for activation of proper stress reactions and maintenance of metabolic homeostasis that have been implicated in life span extension and aging [5]. Cellular programs do the task of maintenance of mitochondrial quality and integrity by monitoring and substituting dysfunctional mitochondria with new

organelles [6]. They necessitate the replication and transcription of mitochondrial protein synthesis, mitochondrial DNA (mtDNA), and separate structural events in the cytoplasm, such as mitochondrial proliferation, mitochondrial autophagy (mitophagy), and mitochondrial fusion/fission [7].

Mutations of mtDNA [8], changed mitochondrial dynamics (mitochondrial fusion/fission, movement, morphology, size, and transport), gene mutations [9], and impaired transcription contribute to mitochondrial dysfunction which results in bioenergetics defects [10]. There are several evidences that prove the importance of the mitochondrial dysfunction in the pathogenesis of diseases such as neurodegenerative disorders [3,11,12]. In addition to this, studies proved that mitochondria have an association with mutated proteins in neurodegenerative diseases [10]. Likewise, there is an interaction between mitochondria and a remarkable amount of disease-specific proteins linked with genetic forms of neurodegenerative diseases. Therefore, treatments targeting at fundamental mitochondrial processes, such as free radical generation or energy metabolism and particular relations of mitochondria with disease-related proteins, show great potential [3].

Mitochondrial Biology and Dynamics

As dynamic organelles, mitochondria are vital for cellular death, life, and differentiation. These also involve in several functions, such as iron/sulfur cluster, amino acid synthesis, and fatty acid metabolism, [13]. While they are best recognized for production of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), they contain numerous other biochemical pathways and also are centers for ion homeostasis [14]. Electron and proton transport is partly done by macromolecular protein complexes, whose subunits are encoded by both mitochondrial and nuclear DNA [13]. Complexes I and III are process main sites in the mitochondrial respiratory chain (RC) [15]. Since its sequencing, 13 proteins encrypted by the mitochondrial genome have been identified and linked to a range of maternally inherited disorders. There are about 1500 mitochondrial proteins encoded by nucleus, although less than half were found with experimental attempts. A molecular framework is provided by a whole inventory of protein for this organelle across tissues for the investigation of mitochondrial pathogenesis and biology [14].

There are two important, opposite forces including mitochondrial fusion and mitochondrial fission which maintain the growth, shape, distribution, and structure of mitochondria [16,17]. The fusion and fission of mitochondria at the organellar level is the primary pathway of quality control (QC), which is vital when the molecular pathways are overpowered [13]. Repetitive cycles of mitochondrial fission and fusion machinery regulate the mitochondria morphology and are crucial for mitochondrial dynamics [18]. Furthermore, mitochondrial dynamics enable the mitochondrial function maintenance and are involved in a mitochondrial QC system by separation or mixing of contents. Various qualities of stress cause various responses from the mitochondrial fission/fusion machinery: low stress triggers mitochondria fusion, prolonged or high stress favors fission [13]. The mitochondrial fission 1 (Fis1) and dynamin-related protein (Drp1) control and regulate fission. The increase in mitochondrial free radicals activates Fis1, which is critical for mitochondrial fission. In contrast, mitochondrial fusion is controlled by three guanosine triphosphatase (GTPase) proteins: two outer membrane localized proteins mitofusin 1 and 2 (Mfn1 and Mfn2) and an inner membrane localized protein optic atrophy 1 (Opa1) [16] (Figure 1).

The balance between fusion and fission rates determines the mitochondria lengths and the degree to which they form closed networks. Pathogenic and metabolic conditions within mitochondria and their cellular environment have effects on these rates [17]. The disproportion between fusion and fission in the mitochondria brings about functional changes, including increased lipid peroxidation, increased reactive oxygen species (ROS) production, decreased membrane potential, decreased respiration, and lower ATP production [16]. The clarification of this network helps understanding the multifaceted biological processes, for example, aging [13]. According to the literature, mitochondria's structural changes, including decreased mitochondrial mixing (fusion) and increased mitochondrial fragmentation (fission), are important factors linked with cell death and mitochondrial dysfunction in aging-related diseases and neurodegenerative diseases [19] (Figure 1).

Mitochondrial fragmentation is the disintegration of one mitochondrion after toxins are applied to the cell and/or when the cell expresses mutant protein(s). This is different from mitochondrial division that is the normal division of a single mitochondrion into two; however, mtDNA synthesis happens in both processes [16]. This abnormality and dysfunction of mitochondrial dynamics happens selectively in the most common chronic age-related and proteopathic neurodegenerative diseases which their manifestation occurred in the brain including Alzheimer's disease (AD) [20], Parkinson's disease (PD) [21], Huntington's disease (HD) [22], and amyotrophic lateral sclerosis (ALS) [23]. Early recognition of mitochondrial dysfunction and abnormal mitochondrial dynamics enables us to interfere in disease processes to restrict disease effects and to change disease progression [16].

Recently, it has been shown that there is a link between mitophagy and mitochondrial dynamics in terms of function [24,25]. Furthermore, mitochondrial fusion and fission have significant parts in disease-related processes, such as mitophagy and apoptosis [17]. The segregation of impaired mitochondria due to fission and consequent inhibition of their fusion mechanism is hypothesized to be a requirement for mitophagic degradation [13]. Finally, it dysfunctional and damaged mitochondria can be removed from the vital network of mitochondria via mitophagy process. This process is seen as representing a very specific pathway of QC that has significant biological relevance and performs at the organellar level [26]. Mitophagy impairments lead to the development of several diseases, such as AD [27], PD [28], HD [29], and ALS [30].

Mitochondrial Dysfunction and Neurodegenerative Diseases

As organelles of eukaryotic cells, mitochondria have several functions, such as synthesis of ATP through energy transduction. On the other hand, ROS are made as by-products of this process which may damage different types of molecules causing mitochondrial dysfunction. Therefore, mitochondrial activity is a double-edged sword which can be both potentially dangerous and essential [13]. Some mitochondrial abnormalities were recognized

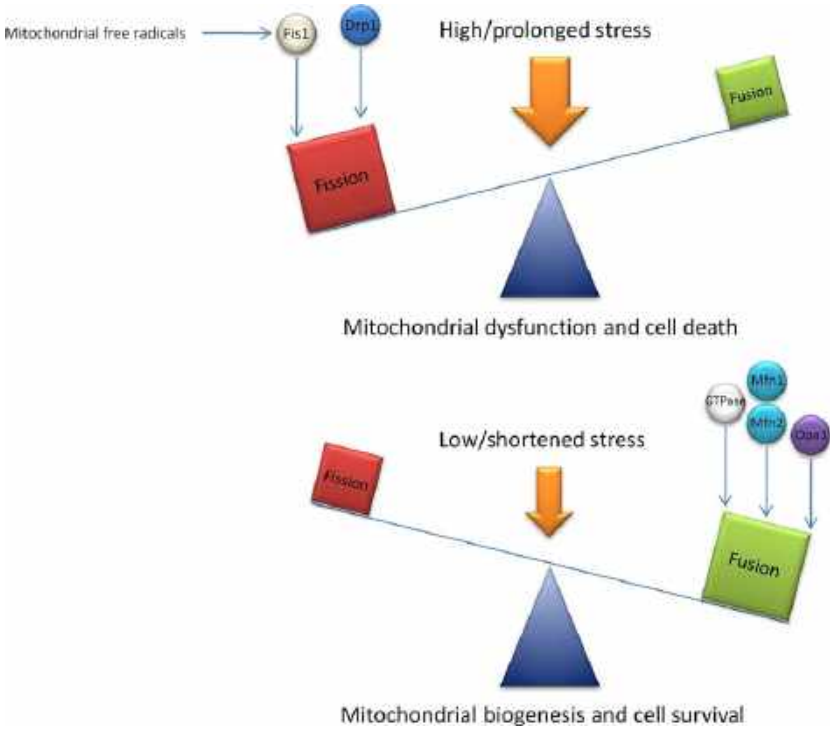

Figure 1 Regulation of mitochondrial quality control by fission and fusion phenomena.

in animal and human models with the metabolic syndrome, such as lower mitochondrial mass [31], altered mitochondrial morphology [32], reduced fatty acid oxidation [33], overproduction of ROS [34], and reduced mitochondrial OXPHOS [35,36]. More than 50 diseases are caused by mitochondrial dysfunction: from neonatal fatalities to cancer [37] and type II diabetes [38], and it is also a possible cause of neurodegenerative diseases [14]. Literature indicates that atypical mitochondrial functions, such as accumulation of mutations that impair mitochondrial protein synthesis occurred in infant mortalities [39]. In addition, mitochondrial decline and mtDNA damage which play crucial roles in the etiology of cancer fall into three main classes: (1) increased accumulation of mtDNA deficiencies, (2) increased mitochondrial oxidative stress and ROS production without ATP depletion, and (3) inhibition of OXPHOS by mtDNA mutations [40]. Likewise, type II diabetes has been related to accumulation of mtDNA proteins synthesis mutations, increased accumulation of mtDNA defects, down regulation of mitochondrial function and gene expression, increased mitochondrial ROS production with ATP depletion, and decreased mitochondrial OXPHOS [41]. Moreover, multiple line of evidence indicated that impaired calcium influx, dissipation of mitochondrial membrane potential, accumulation of mutant proteins in mitochondria, increased accumulation of mtDNA deficiencies, and deficiencies in mitochondrial OXPHOS are significant cellular changes in late-onset neurodegenerative diseases [19] (Table 1).

As mentioned earlier, the dysfunction of mitochondria is linked to the aging as an onset of numerous diseases and it has tremendous cellular consequences [42]. Alterations of mitochondrial activity and number are associated with age-related diseases such as cancer, diabetes, and neurodegenerative diseases [40]. Impaired Ca^{2+} buffering or energy supply, control of apoptosis by mitochondria or increased ROS production can contribute to the progressive decline of long-lived postmitotic cells, such as neurons [43]. Furthermore, mitochondrial ROS generation is known as key factors accountable for cell death and disease progression in age-dependent diseases [16]. Regardless of the main link between human diseases and mitochondrial dysfunction, generally, the molecular causes for dysfunction are poorly understood or even have not been identified [2].

Mitochondria contain multiple electron transporters that can produce a broad network of antioxidant defenses and ROS [44]. Mitochondrial insults, including oxidative damage itself, may lead to an imbalance between ROS production and removal, causing net ROS production [45]. The significance of aging of net production of mitochondrial ROS is supported by evidence that longevity is increased by improving mitochondrial antioxidant defenses [3]. Also, mitochondria is said to play a significant role in neurodegenerative diseases related to aging. Mitochondria are main controllers of cell death, an important characteristic of neurodegeneration. Certainly, aging is the highest risk factor for neurodegenerative diseases, and mitochondria are supposed to speed up aging by the net production of ROS and accumulation of mtDNA mutations. It is hypothesized that somatic mutations of mtDNA developed during aging increase physiological decline that happens with aging and aging-related neurodegeneration [3].

Generally, neurodegenerative diseases are a heterogeneous group of disorders characterized by gradually progressive, selective loss of physiologically or anatomically related neuronal systems. Prototypical examples of the most common chronic neurodegenerative diseases associated with aging and aggregation of misfolded proteins are AD, PD, HD, and ALS. Regardless of this

Table 1 Mitochondrial dysfunction in several diseases

Disease	Mitochondrial abnormalities	Reference
Metabolic syndrome	Reduction in mitochondrial mass Alteration in mitochondrial morphology Decrease in fatty acid oxidation Overproduction of ROS Reduction in mitochondrial OXPHOS	[31–36]
Neonatal fatalities	Accumulation of mutations Impairment of mitochondrial protein synthesis	[39]
Cancer	Increased accumulation of mtDNA deficiencies Increased production of mitochondrial oxidative stress Increased production of mitochondrial ROS without ATP depletion Inhibition of OXPHOS by mtDNA mutations	[40]
Type II diabetes	Accumulation of mtDNA proteins synthesis mutations Increased accumulation of mtDNA defects Downregulation of mitochondrial function and gene expression Increased production of mitochondrial ROS with ATP depletion Reduction in mitochondrial OXPHOS	[41]
Neurodegenerative diseases	Impairment of calcium influx Dissipation of potential mitochondrial membrane Accumulation of mutant proteins in mitochondria Increased accumulation of mtDNA deficiencies Defects of Mitochondrial OXPHOS	[19]

heterogeneity, mitochondrial contribution is probably an central common theme in these disorders [3]. Recently, it was clarified that oxidative damage and mitochondrial dysfunction are main factors in neuronal loss [46]. Free radicals, normally created by mitochondrial respiration, result in oxidative impairment of proteins, carbohydrates, nucleic acids, and lipids. Nevertheless, the mechanism of neuronal death due to oxidative damage is not clear [47]. Cellular injuries, such as oxidative stress, may damage the capacity of cell to make adequate ATP for homeostasis, eventually resulting in necrosis or apoptosis [7]. In several neurological diseases, mitochondrial defects and/or dysfunction in mtDNA are associated with neurodegeneration. There are studies on the role of mitochondria in controlling pathways of apoptotic cell death due to neurodegenerative disease. There is evidence that in brains of patients with neurodegenerative diseases, mitochondria become dysfunctional in tissue by reducing ATP supply and energy production, enhancing generation of ROS, change in calcium buffering, and opening of the mitochondrial permeability transition pore (mPTP) [18].

The majority of ROS production generated in cells by mitochondrial metabolism which implicated in numerous pathological alterations of the CNS including neurodegeneration [48,49]. As mitochondrial metabolism is both principal source of free radicals and high-energy intermediates, it is proposed that acquired or inherited mitochondrial defects can cause neuronal degeneration due to oxidative damage and energy defects. Dysfunction of mitochondrial respiratory chain was reported related to primary mtDNA abnormalities, and in nuclear genes mutations that are directly involved in mitochondrial functions, including paraplegin, surfeit locus protein 1 (SURF1), and frataxin. Increased production of free radical and OXPHOS defects have also been seen in diseases that are not caused by primary abnormalities of mitochondria. The mitochondrial dysfunction in these cases can be an epiphenomenon that could be essential in precipitating a cascade of events causing cell death. Understanding the mitochondria role in the pathogenesis of neurodegenerative diseases can be important for the development of therapeutic strategies in these disorders [50]. Increasing evidence reveals a dominant fundamental role of mitochondrial dysfunction in the neurodegenerative disorders' pathogenesis, including AD, PD, HD, and ALS [1,10,16,19] (Table 2).

Mitochondrial Complexes and Neurodegenerative Diseases

Mitochondria are complex organelles whose dysfunction causes a broad range of diseases [14]. Several studies illustrated that deletions or mutations of single complex subunits, including complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (ubiquinol cytochrome C oxidoreductase), complex IV (cytochrome C oxidase), and complex V (ATP synthase) [69] might have an important effect on the entire complex formation and highlighted the significance of genome coordination for appropriate complex function and assembly [42]. Mitochondrial functions are changed in brains of individuals with certain neurodegenerative disorders [70,71]. Dysfunction of mitochondrial electron transport chain (ETC.) complexes has been associated with the pathogenesis of the most common chronic age-related neurodegenerative diseases which associated with misfolding protein aggregation including AD, PD, HD, and ALS [47,72,73]. It is highlighted that the accumulation of mutant aggregate-prone proteins induced by proteasomal inhibition results in impairment of the mitochondrial respiratory chain complexes activity. In addition, mitochondrial complex deficiencies have an essential role in pathogenesis of AD [74], PD [75], HD [71], and ALS [76] (Figure 2).

Table 2 Main causes of the mitochondrial dysfunction in the most common neurodegenerative diseases

Disease	Abnormalities result in mitochondrial dysfunction	Reference
AD	Deposition of Aβ within mitochondria in the brain of patients with AD	[51–54]
	Impairment of mitochondrial OXPHOS in the brain of patients with AD	
	Downregulation of PGC-1 in the brain of patients with AD	
	Modulation of Aβ aggregation cascade through PPAR-γ dysregulation	
PD	Significant reduction in ATP in the putamen and midbrain	[21,55–58]
	Significant reduction in PCr in the putamen	
	Enhanced formation of free radicals	
	Induction of permeability transition	
	Impairment of intracellular calcium homeostasis	
	Induction of Oxidative Stress	
	Downregulation of PGC-1 in the brain of patients with PD	
	Development of neurodegeneration through PPAR-γ dysregulation	
HD	Impairment of mitochondrial function by mHtt	[59–63]
	Downregulation of PGC-1 and its downstream genes	
	Suppression of PPAR-γ activity by recruitment into Htt aggregates	
ALS	Decrease in mitochondrial Ca^{2+} capacity	[64–68]
	Alteration of axonal mitochondria distribution	
	Alteration in mitochondrial morphology	
	Enhanced production of mitochondrial ROS	
	Defects of mitochondrial respiration in the CNS and muscles of patients with ALS	
	Defects of ATP production in the CNS and muscles of patients with ALS	
	Reduction in mtDNA copy number	
	Deficiencies in activity of respiratory chain	
	Downregulation of PGC-1 and its downstream genes	
	Increases in several miRNAs involved in neuromuscular junction and skeletal muscle regeneration	
	Development of neuroinflammation as a ALS hallmark, through PPAR-γ dysregulation	

Impairment of the mitochondrial respiratory chain complexes activity in AD (mitochondrial complex I, III, and IV deficiency), PD (mitochondrial complex I and IV deficiency), HD (mitochondrial complex II, III, and IV deficiency), and ALS, respectively (mitochondrial complex I, II, III, and IV deficiency). The combined mitochondrial complex deficiencies caused by increase in the expression of hyperphosphorylated tau and Aβ plaques, mα-synuclein, mHtt, and mSOD1 result in promoting the accumulation of aggregated/misfolded of these proteins via the proteasome activity inhibition in patients with AD, PD, HD, and ALS, respectively.

Mitochondrial respiratory chain complex I catalyzes transfer of electron from NADH to the ubiquinone pool (Q), with concurrent vectorial pumping of proton through the inner mitochondrial membrane [77]. This complex is one of the main sites in which electrons are released and react with oxygen, resulting in ROS production, thus causing oxidative stress [78]. Complex I deficiency is among the most frequent reasons of mitochondrial disease in humans [79]. Mitochondrial respiratory chain complex II is an essential component of both the Krebs cycle as well as the mitochondrial respiratory chain, which play a critical role for generating ATP [80]. This is the only one of the mitochondrial respiratory chain complexes that is completely encoded by nuclear genes. In complex II, additional electrons from succinate are transferred into the Q [81]. The production or triggering of ROS by the mitochondrial complex II may have either deleterious or beneficial effects based on the (patho)physiological situation. An enhanced production of mitochondrial ROS is related to multiple pathophysiological disorders, such as neurodegenerative diseases [82]. Mitochondrial respiratory chain complex III channels electrons from the Q to cytochrome c, simultaneously pumping protons from mitochondrial matrix space into the intermembrane space [83]. Complex III deficit is a fairly common deficiency of the OXPHOS system, linked with a broad range of neurological disorders [84]. Mitochondrial respiratory chain complex IV or cytochrome c oxidase (COX) is the terminal complex of the electron transport chain. It catalyzes the electron transfer from cytochrome *c* to reduce molecular oxygen (O_2) and form two molecules of water in a reaction that is coupled to proton pumping across the inner mitochondrial membrane. Complex IV deficiencies result in several human clinical phenotypes, with unclear molecular mechanism [85]. Mitochondrial respiratory chain complex V is the fifth enzyme of the OXPHOS system located in the mitochondrial inner membrane [86]. In the mitochondrial matrix, it synthesizes ATP from adenosine diphosphate (ADP) using energy provided by the proton electrochemical gradient [87]. Most individuals with complex V deficit had clinical onset in the neonatal period with multiorgan failure or severe brain damage leading to a high mortality, such as cardiomyopathy and neuromuscular disorders [86].

Mitochondrial Biogenesis and Neurodegenerative Diseases

Mitochondrial biogenesis assumes a critical part to keep mitochondrial homeostasis during the mitochondria life cycle and finally meet the physiological demands of eukaryotic cells [20]. It is proposed that sequential loss of mtDNA amount in long-term

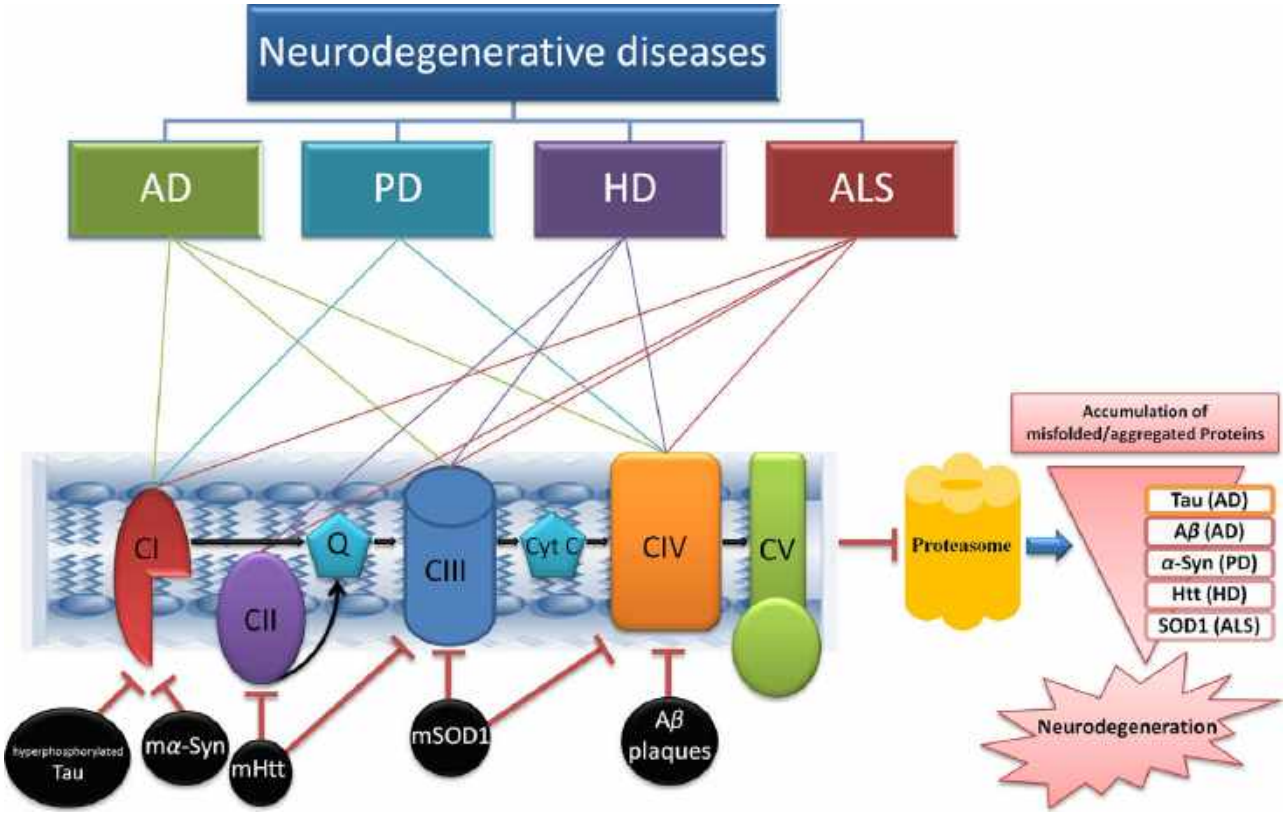

Figure 2 Mitochondrial complex defects in pathogenesis of AD, PD, HD, and ALS.

focal cerebral ischemia points to the failure of mitochondrial renewal mechanisms. Moreover, strong research evidence recommends a probable reduction in ROS production by the biogenesis of a significant density of functional mitochondria [88]. As a highly regulated process, mitochondrial biogenesis requires the participation of both the mitochondrial and nuclear genomes and happens frequently in healthy cells that continually divide and fuse with each other, while in unhealthy cells, division (fission) is leading and after cerebral insults, the mitochondrial network fragments [18]. Increased biogenesis is compatible with the mtDNA copy number and enhanced mitochondrial gene expression. The gene expression profile associated with mitochondrial biogenesis includes peroxisome proliferator-activated receptor-γ coactivator 1 alpha (PGC-1α), mitochondrial transcription factor A (TFAM), nuclear respiratory factor 1 and 2 (NRF1 and NRF2), and mitochondrial transcription factor B1 (TFB1M), [89].

As mitochondria are not synthesized from the beginning, they should proliferate from the ones already existing to keep biogenesis [6]. Their biogenesis appears to be controlled via several processes, including (1) synthesis of outer and inner mitochondrial membranes, (2) synthesis of mitochondrial proteins, (3) synthesis and import of proteins encoded by the nuclear genome, (4) lipid import, (5) oxidative phosphorylation, (6) replication of mtDNA, and (7) mitochondrial fusion and fission [6,90]. Usually, alterations in physiological state including enhanced rates of ATP consumption activate mitochondrial biogenesis for approaching the existing cells capacity to generate it. Some of the main triggers of mitochondrial biogenesis include cell division and repair, embryonic development, alterations in physiological state such as sympathetic stimulation, calorie restriction, exercise, cold stress, energy limitation, hormones (thyroid hormone, leptin, and erythropoietin), and mitochondrial disease/damage such as inflammation, hypoxia/ischemia, and oxidative/nitrosative stress [7]. Mitochondrial damage is reflected by mtDNA impairment and by a decrease in mitochondrial function, mitochondrial RNA (mtRNA) transcripts, and protein synthesis [18].

Multiple investigations offer that disruption of mitochondrial function considered as a critical cause in the pathophysiology of numerous neurological disorders, and adaptive mitochondrial biogenesis has been studied in the nervous system [91]. Reduced mtDNA/nDNA ratio also shows a decreased mitochondrial biogenesis. It is highlighted that impaired mitochondrial biogenesis potentially contributes to the mitochondrial dysfunction and has a significant role in the pathogenesis of the neurodegenerative diseases. Likewise, it should be noted that genes encoding proteins which play a key role in mitochondrial biogenesis are linked with those diseases [20]. Taken together, induction or improvement of mitochondrial biogenesis may be considered as a novel therapeutic target and confirm a modern neuroprotective approach for most of diseases such as neurodegenerative diseases including AD, PD, HD, and ALS in the near future [92] (Figure 3).

Mitochondrial biogenesis as a potential therapeutic approach may use to induce neuroprotection through alleviation of the

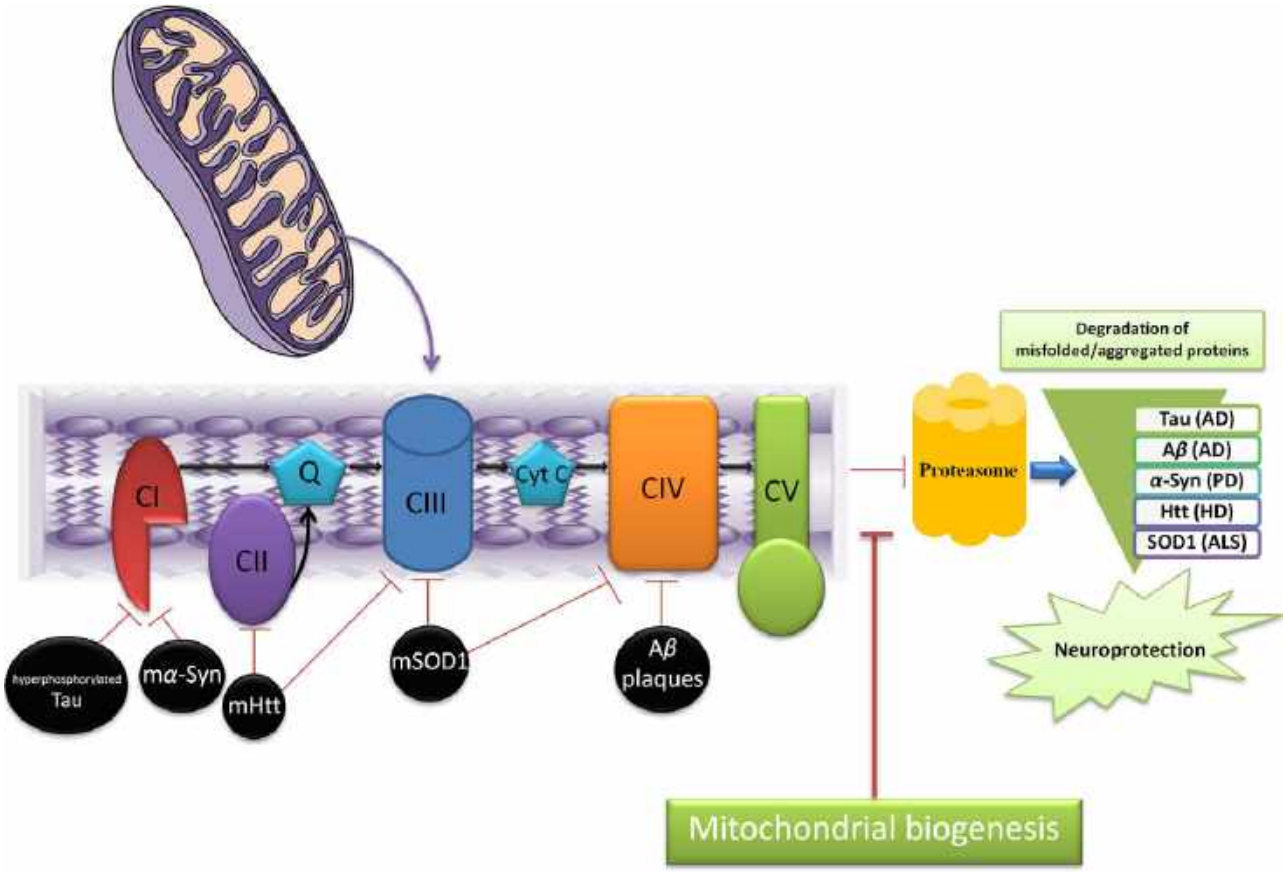

Figure 3 Mitochondrial biogenesis as a novel therapeutic target in treatment of AD, PD, HD, and ALS.

mitochondrial complexes deficiencies that induced by the expression of hyperphosphorylated tau and Aβ plaques, mα-synuclein, mHtt, and mSOD1 in AD, PD, HD, and ALS, respectively. This neuroprotective strategy results in promoting the degradation of aggregated/misfolded of these proteins via the proteasome activity induction.

Transcriptional Approaches to Improve Mitochondrial Function

There are limited number of studies on neuronal mitochondrial biogenesis, but research on other tissues and model systems shows a series of signal transduction proteins, transcription factors, and transcription co-activators should play their crucial roles to regulate mitochondrial mass and number inside neurons [43]. Maintaining effective metabolic output is essentially dependent on regulation of the complex protein-folding environment inside the organelle. Dysregulation of protein homeostasis happens over time via stress induced by the accumulation of ROS and mutations in the mitochondrial genome introduced during replication [42]. Major challenges in cell biology are recognizing all the proteins in this organelle and understanding how they involved in pathways [14]. The dynamics of mitochondrial function and biogenesis is a complex interplay of cellular and molecular processes that ultimately shape bioenergetics capacity. Mitochondrial mass, by itself, represents the net balance between rates of biogenesis and degradation [93].

Mitochondrial biogenesis is dependent on different signaling cascades and transcriptional complexes that promote the formation and assembly of mitochondria. It is a process that is heavily dependent on timely and coordinated transcriptional control of genes encoding for mitochondrial proteins [93]. Biogenesis of mitochondria is regulated mostly at the transcription level, and several nuclear-encoded mitochondrial genes should be expressed in coordination with the 13 mitochondrial-encoded genes. This synchronized bigenomic program comprises of nuclear-encoded mitochondrial proteins that regulate mtDNA replication as well as transcription and also necessitates the induction of mitochondrial DNA polymerase (Polγ), TFAM, and mitochondrial transcription factor B2 (TFB2M) [94,95]. Also, the nuclear regulation mechanisms cause the tissue induction and signal specific subsets of genes that serve particular functions. Most of the mitochondrial proteome is assigned to lineage-specific proteins; therefore, the transcriptional program corresponds to the cell's mitochondrial phenotype and mass to the functions of each tissue and the physiological energy requirements [7].

PGC-1 family members (e.g., PGC-1α and PGC-1β) coactivate genes encoding proteins for transcription and replication of mtDNA as well as importation of mitochondrial protein [7,94,96,97]. They also have contribution in the physiological

integration of mitochondrial biogenesis with oxidative metabolism and provide overlapping and amplifying regulation of several nuclear-encoded mitochondrial genes [98]. As a co-transcriptional regulation factor, the PGC-1α provokes mitochondrial biogenesis by activating several transcription factors, including NRF1 and NRF2. Furthermore, it is called GA-binding protein A (GABPA) that regulates the expression of multiple nuclear genes to encode mitochondrial proteins such as TFAM. The TFAM contributes to the mtDNA maintenance and motivates the replication and transcription of mtDNA as well as PPARs [18,94,99].

As a transcriptional coactivator, PGC-1 functions together with combination of other transcription factors such as peroxisome proliferator-activated receptors (PPARs) in the regulation of mitochondrial biogenesis. PPARs, in particular PPAR-γ, may be a major signaling pathway involved in neuroinflammation [68]. PPAR-γ as a ligand-activated transcriptional factor is a member of the nuclear hormone receptor superfamily. It has effect on the activity or expression of numerous genes in a range of signaling networks, including insulin sensitivity regulation, cell fates, immune responses, fatty acid oxidation, glucose homeostasis, cardiovascular integrity, and redox balance [100]. Likewise, PPAR-γ is known as a main regulatory factor in the target genes modulation with PPAR response element (PPRE) in their promoters, such as those encoding for oxidative stress, inflammation (COX-2), inducible nitric oxide synthase (iNOS), and nuclear factor-kappaB (NF-κB), and apoptosis [68].

In addition, the threonine/serine AMP-activated protein kinase (AMPK) is a master regulator of cellular energy homeostasis that is activated as a consequence of reflecting low energy reserve [101,102]. It stops the continuous progress of ATP-consuming reactions and triggers ATP-generating pathways [103]. AMPK activation results in modulations of several factors like PGC-1α, to produce ATP, while simultaneously stop energy consumption [104]. It is indicated that AMPK activation appears to be essential in the mitochondrial biogenesis [105] through regulating PGC-1α directly [106] or even indirectly by modulating sirtuin 1 (SIRT1) activity [101]. It also inhibits the growth-controlling mammalian target of rapamycin (mTOR) pathway [107,108] by phosphorylation of the tuberous sclerosis 2 (TSC2) tumor suppressor together with the tuberous sclerosis 1 (TSC1) [108]. Activation of the mTOR indicating by Akt/PKB includes the phosphorylation and inactivation of TSC2 [7]. Moreover, Akt/PKB induces mitochondrial biogenesis via the cyclic AMP response element-binding protein (CREB1) and NRF1 phosphorylation, thus allowing target gene activation and nuclear translocation [109].

Mitochondrial biogenesis involves other transcription factors such as sirtuins. Sirtuins (SIRTs) are a family of the nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylases which contribute in numerous cellular processes such as cell cycle, transcription, energy metabolism, mitochondrial functions, aging, apoptosis, and cell survival [104,110,111]. There are seven sirtuins for mammalian with different activities which localized to the nucleus (SIRT1, SIRT6, SIRT7), cytosol (SIRT2), and mitochondria (SIRT3, SIRT4, and SIRT5) [111]. There are several evidence to suggest that sirtuins as the transcriptional regulators may have potential therapeutic effects on a several chronic age-related and aggregate-forming neurodegenerative diseases including AD, PD, HD, and ALS. Sirtuins can influence the progression of neurodegenerative disorders by modulating transcription factor activity [110–112]. It is indicated that SIRT1 induces mitochondrial biogenesis by activating the master regulator PGC-1α [43]. Furthermore, SIRT3 which interacts with mitochondrial complex I is another novel therapeutic target for neurodegenerative diseases [104]. SIRT3 as a downstream target gene of PGC-1α mediates downregulation of the PGC-1α-dependent intracellular ROS production and stimulates mitochondrial biogenesis [113].

There are also many other transcription factors including orphan nuclear estrogen-related receptors (ERRs) which expressed by aerobic tissues. For instance, the estrogen-related receptor alpha (ERRα) is a PGC-1α companion in the genes expression essential for fatty acid β-oxidation [114,115]. Along with CREB1, the Ying–Yang 1 (YY1) transcriptional initiator element-binding protein plays a part in the constitutive expression of respiratory and other energy metabolism genes [116,117]. The myocyte-specific enhancer factor 2A (MEF2A) and the nuclear-encoded proto-oncogene c-Myc are other important genes for mitochondrial biogenesis [118]; these are, respectively, activator of PGC-1β and vital regulator of oxidative capacity in cardiac and skeletal muscle activated by NRF1 [119]. Moreover, MEF2A contributes to activation of stress-induced genes and growth factor and also promotes cell survival as well as cell growth [119].

On the other hand, considerable development has been made in expanding mitochondria-targeted antioxidants, as dysregulation of protein homeostasis induced by the accumulation of ROS and mutations in the mitochondrial genome. Antioxidants protect neurons against mitochondrial functional and structural abnormalities, oxidative damage, and mutant proteins [120]. In the last decade, several antioxidants have been developed such as mitoquinone (MitoQ) as the triphenylphosphonium-based antioxidant as well as Szeto-Schiller 31 and 20 peptides (SS31 and SS20 peptides) as the small peptide-based antioxidants which bind to the inner mitochondrial membrane [120–122].

MitoQ is a form of coenzyme Q which considered as a potential therapeutic antioxidant to protect against mitochondrial oxidative damage by reducing free radicals such as ROS [123] and lead to the neuroprotection against age-related mitochondrial insults [124]. Dumont and his colleagues indicated that MitoQ therapy reduces β-amyloid plaque number and area, amyloid beta-42 (Aβ-42) levels, and brain oxidative stress, as well as improves cognition in a transgenic mouse model of AD [125]. Furthermore, it was found that the combination of creatine and MitoQ shows potential neuroprotective impacts on the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [126]. In addition, administration of MitoQ could extend cell survival and ameliorate motor performance and brain atrophy in a transgenic mouse model of HD [127]. Also, Miquel and his colleagues found modest neuroprotective effects of MitoQ in a mouse model of ALS [128].

Likewise, SS31 and SS20 antioxidant peptides represent a novel therapeutic approach that can scavenge mitochondrial free radicals including ROS and results in inhibition of mitochondrial permeability transition and cytochrome c release which prevents oxidant-induced cell death [104,129,130]. Recently, preclinical studies support potential use of the mitochondria-targeted antioxidants as an effective treatment for neurodegenerative disorders [131]. Manczak and her colleagues stated that SS31 prevents Aβ toxicity as well as decreases learning and memory deficits and

may consider as a potential treatment for AD [132]. Moreover, SS31 and SS20 demonstrated significant neuroprotective effects on dopaminergic neurons of MPTP-treated mice [133]. Likewise, SS31 may use for HD therapy by promoting mitochondrial function and neuronal viability [134]. Additionally, SS31 is a novel therapeutic approach to treat neuronal damage induced by oxidative stress in a mouse model of ALS. It targets the ROS production at the inner mitochondrial membrane and prevents further mitochondrial damage [122].

AD

AD is the most common neurodegenerative disorder marked by progressive loss of memory, characterized by the increased presence of extraneuronal amyloid plaques derived from the proteolytic processing of the amyloid precursor protein (APP) and intraneuronal neurofibrillary tangles (NFTs) made from hyperphosphorylated tau protein (pTau) in the brain. Plaques comprise amyloid beta (Aβ) fibrils that assemble from monomeric and oligomeric intermediates, and are prognostic indicators of AD [135–137]. Recent evidence indicates that mitochondrial dysfunction is a noticeable and early feature of AD with lower energy metabolism as one of the best known primary abnormalities in this disease [20]. They state that intervention at the mitochondrial level could improve Aβ triggered degeneration and dysfunction. This is proved by the *in vivo* evidence of Aβ accumulation inside mitochondria in the brain of patients with AD [51,52]. A plenty of evidence declare that levels of mitochondrial Aβ are related to the degree of cognitive impairment as well as the extent of mitochondrial dysfunction in different regions of brain in AD [51,52,138]. Deposition of Aβ1–40/1–42 in AD cybrids can raise likelihood of mitochondrial dysfunction as well as cell death [51], but the mechanism of Aβ-mediated mitochondrial dysfunction possibly causing neuronal disorder is not exactly clear yet [52]. Additionally, the mitochondrial OXPHOS impairment has been described in the brain of patients with AD by Hauptmann and his colleagues [52]. Interestingly, several researches have shown that PGC-1α as a transcriptional coactivator serves as a regulator of Aβ generation because it affects β-secretase (BACE1) degradation. PGC-1α has been shown to play a significant role in energy metabolism by controlling mitochondrial function in several tissues. The PGC-1 expression considerably reduced in the brain of patients with AD and was involved in the pathological generation of Aβ by influencing the processing of APP; in part by increasing the α-secretase activity [53]. Furthermore, Camacho and his colleagues stated that PPAR-γ can be contributing to the modulation of Aβ aggregation cascade leading to neurodegeneration in Alzheimer's disease [54] (Table 2).

Multiple documents recommended that mitochondrial dysfunction, particularly, deficiencies in mitochondrial respiratory chain complex I has been considered a potential unifying factor in pathogenesis of the neurodegenerative disorders including AD [56,139,140]. Moreover, intracellular NFTs comprised of hyperphosphorylated tau protein as well as extracellular Aβ plaques represent the major hallmarks of AD. Hyperphosphorylated forms of tau selectively impair complex I, lead to increased ROS levels, and result in reduced levels of ATP [141–143]. Clinical and experimental observations suggest that complex I inhibition could contribute to pathogenic mechanisms in some sporadic tauopathies [74] (Figure 2). Furthermore, reduced activity of mitochondrial enzymes, such as complex III, has been reported. Similarly, the mitochondrial complex IV activity is decreased by 70% in patients with AD, which is related to the excitotoxic cell death. It has been stated that a reduction in complex IV activity in the brain associated with aging [72] (Figure 2).

Likewise, it is believed that glutamate excitotoxicity happens in chronic neurodegenerative diseases such as AD [47,72,73]. Insufficient control over glutamate release as a result of mitochondrial complex IV and III deficiency can lead to neuronal cell death. Glutamate release happens mainly through reversal of glutamate transporters of plasma membrane during severe energy stress. Reduction in intracellular ATP leads to depolarization of Ca^{2+} and plasma membrane in glutamate release of from the cytoplasmic pool [72]. The accumulation of mtDNA mutations could be at the origin of ETC. malfunction [3,144]. Moreover, Costa and his colleagues showed that mitochondrial dysfunction has effect on the stress response of endoplasmic reticulum (ER) activated by Aβ peptide (Aβ1–40 isoform) [51,52]. Postmortem research on the AD brain showed that activity of complex IV decreased by 52% in the hippocampus, by 37% in the temporal cortex, and by 27% in the cerebral cortex [72].

The status of this vital feature of mitochondrial function and life in AD is not clear [20,43]. While increased mtDNA, ETC. gene expression and ETC. protein were seen in AD brain [43,145], other studies alternatively indicate a reduction in those in brain of patients with AD [43,146]. Upregulated ETC. genes expression happens in mutant APP transgenic mice and decreased Aβ levels induce mitochondrial biogenesis [147]. Possibly, in different stages of disease, neurons exhibit different forms of mitochondrial biogenesis [148]. It was indicated that Aβ oligomers induce oxidative stress and mitochondria dysfunction, which provoke tau protein hyperphosphorylation and NFTs formation. These events close in on tau protein aggregation and autophagic dysfunction and then lead to neurodegeneration and cell death in AD [149] (Figure 4). Moreover, it was mentioned that expression levels of genes encoding proteins involved in mitochondrial biogenesis such as PGC-1α, NRF1, NRF2, and TFAM have been associated with the neurodegenerative diseases like AD [20]. Expression levels of these genes significantly reduced in both AD hippocampal cells and tissues, proposing a decreased mitochondrial biogenesis [20]. Nevertheless, considering the pleiotropic roles of PGC-1α, it is not clear yet how mitochondrial biogenesis signaling is changed and whether such changes have a hand in mitochondrial dysfunction in AD [20].

Additionally, TFAM plays an important role in the maintenance of mtDNA integrity [150]. It locates on chromosome 10, on which many genes have been reported to be associated with sporadic AD [151]. The moderate likely risk of AD related to TFAM haplotype and genotypes was found [152]. Also in Caucasians, mutations in TFAM contributed to the pathogenesis of sporadic late-onset AD [150]. Moreover, the stimulation of PPAR-γ reduces inflammation in neurological disorders with an inflammatory element such as AD [54]. Recent evidence indicates that PPAR-γ activation modulates Aβ production in cellular models relevant to AD. It shows that PPAR-γ agonists downregulate deposition of Aβ that happens in AD, while its mechanism is still controversial [153]. Together

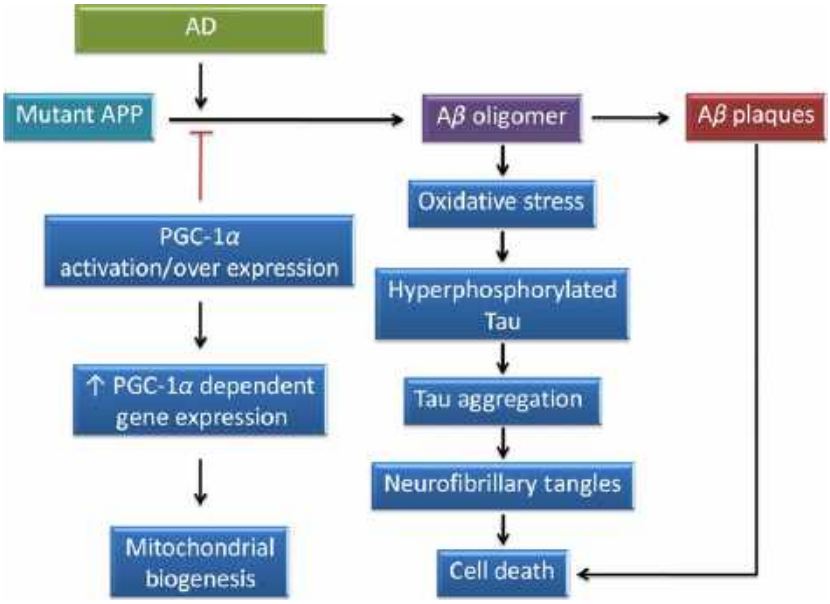

Figure 4 Limitation of the pathological progression, neurodegeneration, and cell death in AD through increasing the PGC-1α activity as a key regulator of the mitochondrial biogenesis.

with this fact, it is hopefully predicted that PPAR-γ may apply as a drug target for the management of neurological disorders like AD [54]. Furthermore, inducing mitochondrial biogenesis by AMPK activation considered as a therapeutic target for AD [154]. In addition, activation of SIRT1 in brain protects against learning impairments and hippocampal degeneration by decreasing the acetylation of the SIRT1 substrates such as PGC-1α which results in PGC-1α activation and also reduction in amyloid pathology in a mouse model of AD [155]. Overall, this data demonstrated mitochondrial biogenesis induction decreases mitochondria dysfunction. Based on data mentioned above, the impaired mitochondrial biogenesis has been suggested as underlying factor in mitochondrial dysfunction in AD and increasing mitochondrial biogenesis may represent a possible pharmacologic strategies for the AD treatment [20].

PD

PD is a progressive neurological movement disorder linked to uncertain etiology having possible effects of genetic-environmental factors [156]. However, the cellular mechanisms that result in cell death in the nigrostriatal system in PD are still unclear [157,158], it is generally accepted that the causes of PD are mainly mitochondrial dysfunction, oxidative stress, chronic inflammation, aberrant protein folding, and abnormal protein aggregation [89,159,160]. The significant reduction in ATP and phosphocreatine (PCr) in the putamen and the significant reduction in ATP in the midbrain as high energy metabolites are indicative of mitochondrial dysfunction in the mesostriatal dopaminergic neurons in early and advanced PD [21]; however, reduction in the ATP production is not just the outcome of mitochondrial dysfunction. In addition, there are other potentially deleterious events such as enhanced formation of free radicals, induction of permeability transition, impaired intracellular calcium homeostasis, and oxidative stress, which in predispose affected cells to necrosis or apoptosis depending on the rate of consumption and depletion of ATP [55,56]. Prohibition of mitochondrial respiratory chain may result in incomplete consumption of O2, decreased of ATP, and increased free radical formation. Free radicals directly inhibit the respiratory chain of mitochondria, which can cause a detrimental cycle that results in oxidative cell damage [161]. Several mutations in mitochondrial proteins encoded by nuclear and mitochondrial genes were linked with idiopathic and familial types of PD [71]. A genomewide examination of controls and patients with PD showed that expression of PGC-1α as a master controller of mitochondrial biogenesis was decreased in patients with PD [57] and this can confirm vital roles of mitochondrial dysfunction in the PD pathogenesis. Moreover, dysregulation of PPAR-γ is linked to the development of neurodegenerative diseases with an inflammatory component-like PD [58] (Table 2).

In this regard, several postmortem studies have shown a meaningful decline in the mitochondrial complex I activity as well as coenzyme Q10, ubiquinone, and also complex IV in the substantia nigra of PD brains [162–164] (Figure 2). Complex I deficit is the most common cause of rare diseases of respiratory chain [14] as well as endogenous and environmental oxidative stressors underlying mitochondrial dysfunction observed in neurodegenerative diseases including PD [89,164]. The latest study revealed that activity of complex I is decreased in postmortem brain tissue of patients with PD as a consequence of oxidative damage that leads to instability and loss through degradation of at least one subunit [164]. Particularly, loss of activity of complex I at the mitochondrial ETC. has been observed in idiopathic PD [165]. Activity of complex I is decreased in the substantia nigra of patients with PD, which may encourage the accumulation of protein inclusions (Lewy bodies) containing α-synuclein (α-syn) [166,167].

Moreover, complex I inhibitors including neurotoxins, such as MPTP which transformed to 1-methyl-4-phenylpyridinium (MPP^+) and 6-hydroxydopamine (6-OHDA), and also pesticides, like rotenone and paraquat cause neuropathological changes similar to PD. Studies on postmortem brains of patients with PD suggested that not only levels of numerous mitochondrial proteins

are changed, but also genetic mutations happen in familial PD-linked genes which may alter mitochondrial function [166]. There is evidence that mitochondrial dysfunction is a main PD initiator, because it has been reported that complex I inhibition results in the formation of α-syn positive cytoplasmic inclusions in cellular and animal PD models [168]. As the α-syn overexpression causes parkinsonism together with the nigrostriatal pathway degeneration, the complex I dysfunction is the most probable cause of PD by modulating the accumulation of misfolded proteins, perhaps via the proteasome inhibition [75,169] (Figure 2). In animal models of PD (e.g., rodents and primates), for example, administration of complex I inhibitors can replicate several key features of sporadic PD, comprising of selective degeneration of dopaminergic neurons in substantia nigra, aggregation and overproduction of α-syn, accumulation of Lewy body-like intraneuronal inclusions, increase in ROS generation, and impairment of behavioral function, which results in irreversible parkinsonism [42,170].

Several lines of evidence represent that the deficit in PD is at or above the level of PGC-1α expression, which in turn regulates function of complex I mitochondrial ETC. [171]. Lately, varied proteins involved in familial PD, including α-syn, parkin, PTEN-induced putative kinase 1 (PINK1), protein deglycase DJ-1 (parkinson disease protein 7), and leucine-rich repeat kinase 2 (LRRK2 or dardarin), have been associated with quality control and regulating mitochondrial dynamics [172,173]. In cellular disease models, PGC-1α activation leads to higher expression of nuclear-encoded subunits of the mitochondrial respiratory chain and stops the dopaminergic neuron loss induced by the pesticide rotenone or mutant α-syn [174]. Interestingly, parkin and PINK1 have been implicated in regulating mitochondrial biogenesis [175]. Parkin has a part in mitochondrial biogenesis [176,177] by controlling both replication and transcription of mtDNA in proliferating cells. It increases mitochondrial replication, expressions, and transcription of respiratory chain complexes [177]. Degradation of parkin-interacting substrate (PARIS) by parkin raises expression of PGC-1α-dependent genes and biogenesis of mitochondria [178]. In a neurotoxin mouse model of PD, PGC-1α overexpression in neurons was protective [57]. Consequently, loss of parkin function blocks mitochondrial biogenesis via PARIS accumulation [179]. On the other hand, PINK1 is processed by healthy mitochondria and released to trigger neuron differentiation [180]. It is thought to facilitate the binding of parkin protein into depolarized mitochondria to induce mitophagy/autophagy and protect cells from stress-induced mitochondrial dysfunction [181,182]. Gegg and his colleagues reported a vital role of PINK1 in maintaining mitochondrial ETC. activity as well as mitochondrial biogenesis. They showed their dysfunction was involved in sporadic types of PD. Thus, PINK1 expression loss led to reduced levels of mtDNA, mitochondrial biogenesis and mtDNA synthesis [183]. Likewise, the mitochondrial protein DJ-1, as an antioxidant which plays a role in the maintenance of the complex I activity, has been reported to stabilize Nrf2 [184], but mutations in DJ-1 associated with enhancement of the α-syn aggregation, oxidative stress, and possibly cellular apoptosis [185]. In addition, mutation of LRRK2 may result in abnormal phosphorylation of mitochondrial proteins which induces apoptotic cell death [185] (Figure 5).

Moreover, there is an association between TFAM and parkin. As mitochondrial import of parkin was increased in the presence of mitochondrial extract or TFAM, some proteins including TFAM have a part in the export and/or the import of parkin [177]. TFAM–parkin complex associated with PD pathogenesis bound to mtDNA control area and enhanced mitochondrial biogenesis [177,186]. Additionally, involvement of TFAM as a multifunctional mtDNA metabolism regulator in pathogenesis of PD (*in vitro* and *in vivo* models of PD) directly and indirectly confirmed via increase in mitochondrial respiratory functions and protection from oxidative stress [186]. It is also stated that gene therapy based on transfection of mtDNA-complexed TFAM or recombinant TFAM to cybrid cells of PD led to noticeable improvement of different mitochondrial functions [186,187]. Furthermore, recent investigations have described a new role for PPAR-γ receptors in the regulation of inflammation [188]. Regarding with these

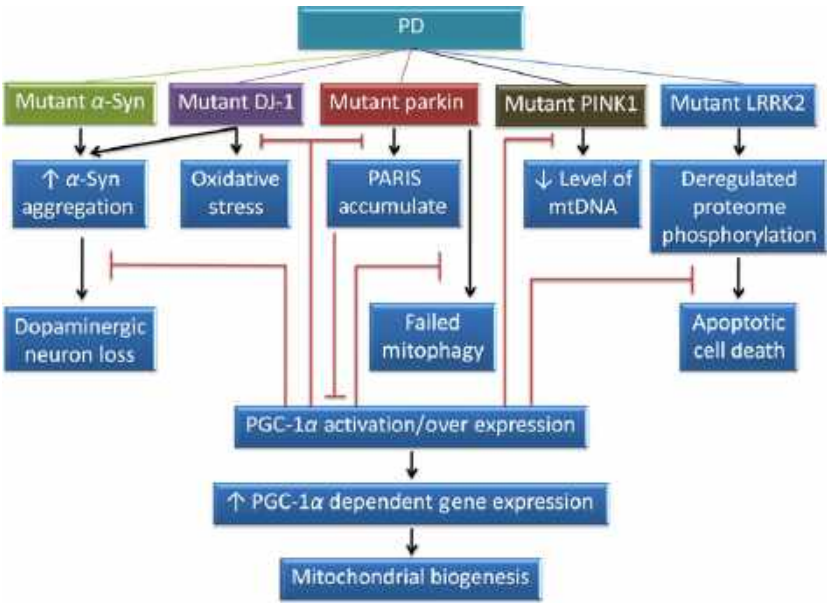

Figure 5 Limitation of the pathological progression, neurodegeneration, and cell death in PD through increasing the PGC-1α activity as a key regulator of the mitochondrial biogenesis.

reports, PPAR-γ agonists have been shown to attenuate inflammatory responses in brain as well as animal models of neurodegenerative diseases such as PD which is associated with a considerable degree of neuroinflammation [189]. Recently, the antiinflammatory role of PPAR-γ agonists in mouse models of PD measured by reductions in both microgliosis and astrogliosis. Thus, PPAR-γ may be beneficial for treating the brain disorders with an inflammatory component-like PD [190]. Likewise, it has been suggested that AMPK activation as a therapeutic approach may promote neuroprotection in PD by mediating mitochondrial biogenesis [191]. Moreover, a recent article shown that activation of SIRT1 induces neuroprotection against α-syn aggregation by activating PGC-1α as well as molecular chaperones in mice model of PD [192]. Indeed, the pathway of mitochondrial biogenesis has come as a possible healing target for PD.

HD

HD is an inherited and an autosomal dominant disorder characterized by psychiatric disturbances, cognitive deterioration, and motor impairment. HD as a fetal neurodegenerative disease caused by the development of cytosine–adenine–guanine (CAG, translated into glutamine) triplet repeats in the huntingtin (Htt) gene (also called HD) and characterized by accumulation of insoluble polyglutamine-containing Htt protein aggregated in affected neurons [71,193,194]. Mitochondrial dysfunction is strongly associated with the pathogenesis of HD [195–197]. Cui and his colleagues reported that genetic elimination of PGC-1α increases HD progression, as measured by the observing striatal neurodegeneration and motor coordination [62], which pinpoints the vital contribution of PGC-1α in HD [196]. Also, it was found that PGC-1α as a key factor involved in the regulation of multiple pathways such as mitochondrial biogenesis and OXPHOS is downregulated in HD [61,62]. Thus, it was suggested that a deficiency in PGC-1α and downstream genes may lead to mitochondrial dysfunction in HD, including muscle [198], fat tissue [199], as well as brain [200]. Likewise, several downstream targets of PGC-1α such as NRF1 and NRF2, and TFAM can increase the HD mitochondrial dysfunction [201]. Also, several studies revealed that mutant huntingtin (mHtt) impaired mitochondrial functions in mHtt-expressing striatal cells [59,60]. In turn, mHtt expression suppresses the PPAR-γ transcriptional activity, which is important for mitochondrial stabilization [63]. Decrease in the available PPAR-γ protein by recruitment into Htt masses results in mitochondrial dysfunction [61,195,196] (Table 2).

Additionally, it has been indicated that mitochondrial ATP levels and ETC. activity are reduced in patients with HD [166]. In late-stage patients with HD, decreased activity of several OXPHOS components, including mitochondrial complexes II, III, and IV, has been reported through biochemical research on mitochondria in striatal neurons [202]. Further, in research on knock-in and HD transgenic mice as well as experimental models of HD rodent, reductions of enzyme activities of complexes I, II, III, and IV were seen in brain tissues [203], suggesting that mitochondria contribute to HD pathogenesis [202]. In addition, significant declines of mitochondrial activities in complex I, II, III, and IV have been reported in the neostriatum of HD patients' brains [202,204] (Figure 2). Decreases of complex II/III activity happen in the brain areas affected by the HD pathogenesis; reduced complex II/III activity in the putamen (by 67%) and caudate (by 29%) was seen in postmortem brain tissue, and activity of complex IV was decreased in both regions by 62% and 30%, respectively [72,205]. The activities of mitochondrial complex III and IV are linked with excitotoxic cell death and reduced by 30% in this disorder [72].

Another potential cause of mitochondrial dysfunction in HD brains is the toxic effects of mutant Htt that result in those changes in mitochondrial complex activities [71]. In the postmortem on patients with HD, the main hypothesis behind abnormalities in the mitochondrial respiratory chain reveals that they are indirectly or directly caused by the toxic mHtt expression [59,148]. On one hand, mHtt produces HD-like symptoms by interrupt complex II activity and mitochondrial Ca^{2+} buffering [206]. On the other hand, expression of mHtt selectively damages the complex III activity and promotes the accumulation of aggregated/misfolded Htt proteins via the proteasome activity inhibition in patients with HD (Figure 2). The presence of such feedback systems, containing mitochondrial complex III, proteasome, and misfolded/aggregated Htt proteins suggests that increasing the mitochondrial respiratory, particularly, activity of complex III, can slow down or even prevent the HD progression [71,202]. A clue clarifying the impacts of complex III inhibitors on the Htt aggregates was taken from the evidence that only complex III inhibitors damaged chymotrypsin-like activity of proteasomes in a ROS-independent manner. Complex III inhibitors selectively promoted the accumulation of Htt aggregates. As other respiratory inhibitors had no considerable effect on the formation of Htt aggregates, the depletion of ATP does not simply explain the effects of complex III inhibitors [71,202].

There are several documents about the PGC-1α role in mitochondrial impairment in HD and its potential as a therapeutic target to treat HD [207]. Over the past few years, studies have shown an impaired function of PGC-1α as a causing of the mitochondrial dysfunction in HD [207]. Impaired PGC-1α levels and function happen in transgenic mice and mouse HD models, striatal cell lines, and also in postmortem brain, myoblasts as well as muscle tissues of patients with HD [200,208]. Indeed, genetic elimination of PGC-1α causes enhanced progression of HD, as evaluated by the observing neuronal neurodegeneration and motor coordination [62,201], which indicates the important contribution of PGC-1α in HD [201]. Moreover, several downstream targets (NRF1, NRF2, and TFAM) of PGC-1α may be involved in the mitochondrial dysfunction of HD [201]. A pathologic grade-dependent significant decrease in mitochondria numbers in striatal spiny neurons was shown by Kim et al., which was associated with decreases in TFAM and PGC-1α [204]. Moreover, significant decreases in TFAM and PGC-1α have been reported in both myoblast cultures and muscle biopsies from patients with HD [62,204]. These findings robustly pinpoint decreased expression of PGC-1α in HD pathogenesis [208].

Interestingly, PGC-1α promoted removal of protein aggregates and Htt turnover by transcription factor EB (TFEB) activation. TFEB as a main regulator of the autophagy–lysosome pathway is able of decreasing neurotoxicity as well as Htt aggregation, placing PGC-1α upstream of TFEB and recognizing these two molecules as substantial therapeutic targets in HD and possibly other

neurodegenerative disorders resulted from protein misfolding [209] (Figure 6). Quintanilla and his colleagues indicated that activation of PPAR-γ receptors can ameliorate mitochondrial dysfunction in mHtt-expressing cells, which has a significant role in the HD pathogenesis [195]. PPAR-γ agonists prevent oxidative stress and attenuate dysfunction of mitochondria in mHtt striatal cells [197] and also challenged with a calcium overload in mHtt-expressing cells. In addition, PPAR-γ agonists enhance oxidative capacity of phosphorylation in human and mouse cells and increase mitochondrial biogenesis [210,211]. It was demonstrated that PPAR-γ agonists could represent a new objective for the advance of therapeutic plans for HD [195]. Likewise, AMPK activation induces neuroprotection in HD through promoting mitochondrial biogenesis and elevating cell survival [111]. Additionally, overexpression of SIRT1 improves motor function and attenuates mHtt-mediated metabolic abnormalities by activating PGC-1α in transgenic mouse models of HD [212]. These results propose that the biogenesis pathway of mitochondria can be a potential novel therapeutic target for HD treatment.

ALS

ALS is a progressive adult-onset neurodegenerative disorder that leads to fatal paralysis. Disease in humans and rodent models initiates with muscle denervation and muscle atrophy following denervation, each arising from degeneration and selective loss of motor neurons in the spinal cord as well as brain [64]. Several studies reported that in ALS, mitochondria play as a target for toxicity through decreased mitochondrial Ca^{2+} capacity, altered distribution of axonal mitochondria, abnormal mitochondrial morphology, elevated levels of mitochondrial ROS production, deficits in mitochondrial respiration, and ATP production in the CNS as well as muscles of patients with ALS [64]. Morphological and biochemical mitochondrial abnormalities including a reduction in mtDNA copy number and deficiencies in activity of respiratory chain were confirmed in postmortem spinal cords of patients with ALS [65]. Specific damage of muscle or neurons can clearly be caused by dysfunction of mitochondria, because mutation/deletion in mitochondrial genes leads to specific muscle and nerve diseases [66]. In patients with ALS, mitochondrial dysfunction of skeletal muscle is linked with a decrease in mRNA of the PGC-1α and PGC-1β, NRF1, ERRα, Mfn1 and Mfn2, and protein content as well as increases in several miRNAs possibly involved in neuromuscular junction and skeletal muscle regeneration. It suggests that mitochondrial dysfunction in skeletal muscle plays key roles in the pathogenesis of ALS [67]. In addition, it was reported that PPAR-γ might be a main signaling pathway contributing to neuroinflammation, which is considered as one of the hallmarks of ALS [68] (Table 2).

Several previous studies reported changes in mitochondrial ETC. activities in ALS [213]. For instance, increased activity of complex I found in postmortem brain tissue may indicate a compensatory incident against the deficit of complex IV enzymes encoded by mtDNA which seen in some patients with ALS. Nevertheless, in postmortem spinal cord tissue from sporadic ALS (sALS) and familial ALS (fALS) cases, a reduction in citrate synthase activity is paralleled by reduction in the activities of complexes I + III, II + III, and IV, which might be seen after a selective loss of mitochondria in spinal cords or increased damage of mtDNA [23] (Figure 2). Moreover, higher levels of oxidized ETC. cofactor Q10 in sALS cerebrospinal fluid and also increased levels of lactate and ROS in their blood have been seen [214]. Likewise, oxidative stress has contributed as a part of the pathogenic pathway in ALS and might derive from defective OXPHOS [215].

In addition, ALS has been linked with over 130 different mutations in the Cu/Zn superoxide dismutase (SOD1) gene, yet this toxicity mechanism is still controversial. While it is not completely clear how mitochondria is damaged by mutant SOD1 (mSOD1), some recent research has revealed that ALS-linked SOD1 mutations are recruited selectively to mitochondria and induce respiratory deficiencies [65]. It is also highlighted that accompanying mSOD1-mediated disease is evidence for alteration of mitochondrial calcium-loading capacity, impairment of electron transport

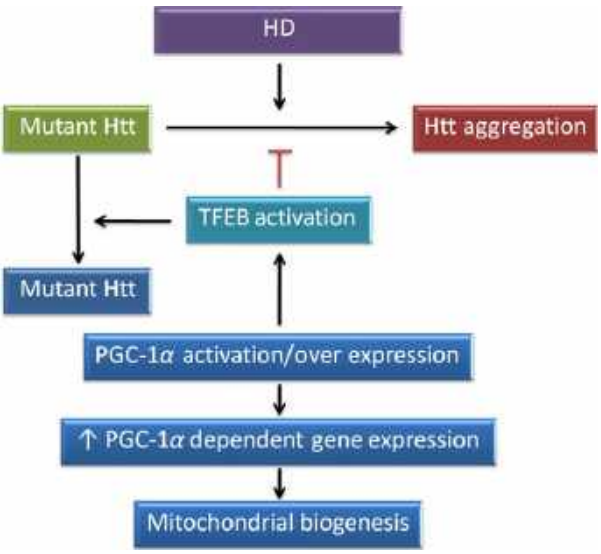

Figure 6 Limitation of the pathological progression, neurodegeneration, and cell death in HD through increasing the PGC-1α activity as a key regulator of the mitochondrial biogenesis.

chain activities particularly in complexes III, increase in aberrant ROS production, and block both protein import at the mitochondrial outer membrane and the antiapoptotic actions of B-cell lymphoma (2BCL2) [66]. Likewise, changes in the activities of respiratory chain complexes were defined in sporadic ALS, exhibiting higher activity of complexes I and II/III in the frontal cortex of SOD1-related patients with ALS, and reduced activity of complex IV in the spinal cord and individual spinal motor neurons [76]. Menzies et al. (2002) reported a particular reduction in activity of complex IV in motor neurons of spinal cord from sporadic cases of ALS [76] (Figure 2).

Denervation-induced muscle atrophy is considered to be an early event along with changes in mitochondrial morphology and activity within muscle in ALS [64]. A significant decrease in mRNA of the PGC-1α and PGC-1β, NRF1, ERRα, Mfn1 and Mfn2, protein content as well as subunit IV of the COX mRNA and protein was seen in patients with ALS [67]. In patients with ALS, mitochondrial dysfunction of skeletal muscle is related to a decrease in PGC-1α signaling networks involved in mitochondrial function and biogenesis [67]. The PGC-1α promoted several effects on muscle, such as enhanced mitochondrial activity and mass (Figure 7). Mitochondrial activity and biogenesis are retained via end-stage disease, together with maintenance of muscle function, delayed muscle atrophy, and considerably improved muscle tolerance even at late stages of disease. Nevertheless, survival was not prolonged; drugs increasing activity of PGC-1α in muscle show a great treatment for retaining muscle function during ALS progression [64].

Another possible method to activate the pathway of PGC-1α, and improving mitochondrial function is through PPARs activation which interact with PGC-1α and work together with combination of this transcriptional coactivator in the regulation of mitochondrial biogenesis [68]. PPAR-dependent self-protective mechanisms appear to be relevant for survival of ALS motor neurons [216]. PPARs especially PPAR-γ may be main regulators of neuroinflammation signaling seen in ALS and perhaps a new target for the development of ALS therapeutic strategies. Because neuroinflammatory pathway is one of the hallmarks of ALS, thus, neuroinflammation blockage may have a therapeutic effect on patients with ALS [64,68]. Likewise, inducing mitochondrial biogenesis by AMPK activation may present a promising therapeutic approach in mutant SOD1 mice model of ALS [217]. Recently, it was also shown that activation of SIRT1 enhances the survival of motor neurons by activation of PGC-1α in transgenic mice model of ALS [155]. In addition, a recent article identified that SIRT3 protect against mitochondrial fragmentation and neuronal cell death in ALS pathogenesis using a cell-based model [111]. Altogether, these observations strongly suggest that fine-tuning PPAR-γ transcriptional activity within the CNS may represent an novel approach to limit the progression of ALS [216].

Conclusion

As highly dynamic organelles, mitochondria have crucial roles in cell survival as well as cell death [1,2] and able to alter their morphology, number, and function in reaction to stressors and physiological conditions [2]. The morphology of mitochondria is controlled by repetitive cycles of mitochondrial fusion and fission machinery which are central to mitochondrial dynamics [18]. Altered mitochondrial dynamics as well as mDNA mutations [8], gene mutations [9], impaired transcription contribute to mitochondrial dysfunction [10] which results in the pathogenesis of several diseases [3,11,12]. Dysfunction and abnormality in mitochondrial dynamics, such as reduced mitochondrial mixing (fusion) and increased mitochondrial fragmentation (fission), are important factors related to the mitochondrial dysfunction, cell death in aging [19], and neurodegenerative diseases, including AD [20], PD [21], HD [22], and ALS [23]. Mitochondrial dysfunction is reflected by mtDNA damage and decrease in mitochondrial function, mtRNA transcripts, and protein synthesis [18]. Mitochondrial functions are changed in brains of individuals with specific neurodegenerative disorders [70,71]. In addition, dysfunction of ETC. complexes was involved in the pathogenesis of chronic neurodegenerative diseases [72,73]. Regarding these data, mitochondria considered as a potential target for pharmacological-based therapies [92].

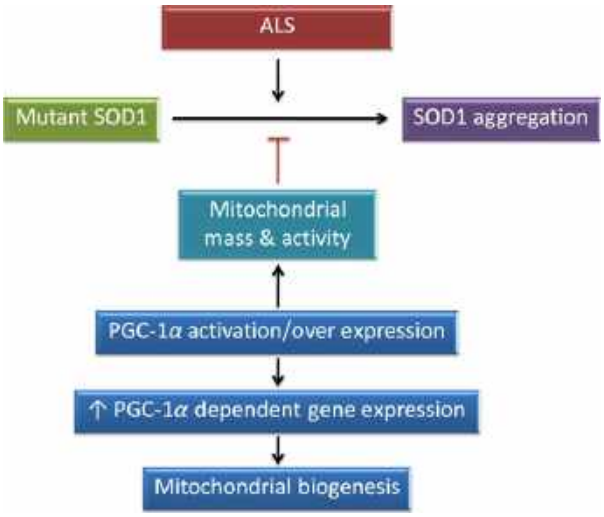

Figure 7 Limitation of the pathological progression, neurodegeneration, and cell death in ALS through increasing the PGC-1α activity as a key regulator of the mitochondrial biogenesis.

Several lines of evidence demonstrate that mitochondrial biogenesis has a vital role in maintaining mitochondrial homeostasis to meet the physiological requirements of eukaryotic cells [20]. Enhanced biogenesis is compatible with the mtDNA copy number and increased mitochondrial gene expression contributed to mitochondrial biogenesis, including PGC-1α, PGC-1β, TFAM, NRF1, NRF2, TFB1M, and PPAR-γ [89]. Accordingly, the impaired mitochondrial biogenesis is associated with the mitochondrial dysfunction and has a significant role in the pathogenesis of the neurodegenerative disorders [148]. Overall, this data demonstrated induction or improvement of mitochondrial biogenesis alleviates mitochondrial dysfunction and may confirm a modern neuroprotective approach in the near future [91]. Altogether, it is strongly suggested that fine-tuning of transcriptional activities of the mitochondrial biogenesis regulators within the CNS may represent attractive approaches to limit the progression of neurodegenerative diseases.

Acknowledgments

This work was supported by a grant (DIP-2012-026) from the Universiti Kebangsaan Malaysia fund.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Filosto M, Scarpelli M, Cotelli MS, et al. The role of mitochondria in neurodegenerative diseases. *J Neurol* 2011;**258**:1763–1774.
2. Verdin E, Hirschey MD, Finley LWS, Haigis MC. Sirtuin regulation of mitochondria: Energy production, apoptosis, and signaling. *Trends Biochem Sci* 2010;**35**:669–675.
3. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 2006;**443**:787–795.
4. Golpich M, Amini E, Hemmati F, et al. Glycogen synthase kinase-3 beta (GSK-3β) signaling: Implications for Parkinson's disease. *Pharmacol Res* 2015;**97**:16–26.
5. Bernier M, Paul RK, Martin-Montalvo A, et al. Negative regulation of STAT3 protein-mediated cellular respiration by SIRT1 protein. *J Biol Chem* 2011;**286**:19270–19279.
6. Okamoto K, Kondo-Okamoto N. Mitochondria and autophagy: Critical interplay between the two homeostats. *Biochim Biophys Acta* 2012;**1820**:595–600.
7. Piantadosi CA, Suliman HB. Redox regulation of mitochondrial biogenesis. *Free Radic Biol Med* 2012;**53**:2043–2053.
8. Hiona A, Sanz A, Kujoth GC, et al. Mitochondrial DNA mutations induce mitochondrial dysfunction, apoptosis and sarcopenia in skeletal muscle of mitochondrial DNA mutator mice. *PLoS One* 2010;**5**:e11468, doi: 10.1371/journal.pone.0011468.
9. McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. *Lancet Neurol* 2010;**9**:829–840.
10. Chaturvedi RK, Beal MF. Mitochondrial diseases of the brain. *Free Radic Biol Med* 2013;**63**:1–29.
11. Yao J, Irwin RW, Zhao LQ, Nilsen J, Hamilton RT, Brinton RD. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 2009;**106**:14670–14675.
12. Neustadt J, Pieczenik SR. Medication-induced mitochondrial damage and disease. *Mol Nutr Food Res* 2008;**52**:780–788.
13. Fischer F, Hamann A, Osiewacz HD. Mitochondrial quality control: An integrated network of pathways. *Trends Biochem Sci* 2012;**37**:284–292.
14. Pagliarini DJ, Calvo SE, Chang B, et al. A mitochondrial protein compendium elucidates complex I disease biology. *Cell* 2008;**134**:112–123.
15. Brand MD. The sites and topology of mitochondrial superoxide production. *Exp Gerontol* 2010;**45**:466–472.
16. Calkins MJ, Reddy PH. Assessment of newly synthesized mitochondrial DNA using BrdU labeling in primary neurons from Alzheimer's disease mice: Implications for impaired mitochondrial biogenesis and synaptic damage. *Biochim Biophys Acta* 2011;**1812**:1182–1189.
17. van der Bliek AM, Shen QF, Kawajiri S. Mechanisms of mitochondrial fission and fusion. *Cold Spring Harbor Perspect Biol* 2013;**5**:a011072, doi: 10.1101/cshperspect.a011072.
18. Sharma J, Johnston MV, Hossain MA. Sex differences in mitochondrial biogenesis determine neuronal death and survival in response to oxygen glucose deprivation and reoxygenation. *BMC Neurosci* 2014;**15**:1–14.
19. Reddy PH, Reddy TP. Mitochondria as a therapeutic target for aging and neurodegenerative diseases. *Curr Alzheimer Res* 2011;**8**:393–409.
20. Sheng B, Wang X, Su B, et al. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. *J Neurochem* 2012;**120**:419–429.
21. Hattingen E, Magerkurth J, Pilatus U, et al. Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. *Brain* 2009;**132**:3285–3297.
22. Reddy PH, Shirendeb UP. Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease. *Biochim Biophys Acta* 2012;**1822**:101–110.
23. Cozzolino M, Carri MT. Mitochondrial dysfunction in ALS. *Prog Neurobiol* 2012;**97**:54–66.
24. Tanaka A, Cleland MM, Xu S, et al. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. *J Cell Biol* 2010;**191**:1367–1380.
25. Westermann B. Mitochondrial fusion and fission in cell life and death. *Nat Rev Mol Cell Biol* 2010;**11**:872–884.
26. Youle RJ, Narendra DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol* 2011;**12**:9–14.
27. Ding Y, Gao H, Zhao L, Wang X, Zheng M. Mitofusin 2-deficiency suppresses cell proliferation through disturbance of autophagy. *PLoS One* 2015;**10**:e0121328, doi: 10.1371/journal.pone.0121328.
28. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. *Science* 2011;**333**:1109–1112.
29. Qin Z-H, Wang Y, Kegel KB, et al. Autophagy regulates the processing of amino terminal huntingtin fragments. *Hum Mol Genet* 2003;**12**:3231–3244.
30. Braun RJ. Mitochondrion-mediated cell death: Dissecting yeast apoptosis for a better understanding of neurodegeneration. *Front Oncol* 2012;**2**:1–14.
31. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* 2002;**51**:2944–2950.
32. Civitarese AE, MacLean PS, Carling S, et al. Regulation of skeletal muscle oxidative capacity and insulin signaling by the mitochondrial rhomboid protease PARL. *Cell Metab* 2010;**11**:412–426.
33. Zhang D, Liu Z-X, Choi CS, et al. Mitochondrial dysfunction due to long-chain Acyl-CoA dehydrogenase deficiency causes hepatic steatosis and hepatic insulin resistance. *Proc Natl Acad Sci* 2007;**104**:17075–17080.
34. Hirschey M, Shimazu T, Huang J-Y, Schwer B, Verdin E, editors. *SIRT3 regulates mitochondrial protein acetylation and intermediary metabolism. Cold Spring Harbor symposia on quantitative biology*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2011.
35. Petersen KF, Dufour S, Shulman GI. Decreased insulin-stimulated ATP synthesis and phosphate transport in muscle of insulin-resistant offspring of type 2 diabetic parents. *PLoS Med* 2005;**2**:e233.
36. Befroy DE, Petersen KF, Dufour S, et al. Impaired mitochondrial substrate oxidation in muscle of insulin-resistant offspring of type 2 diabetic patients. *Diabetes* 2007;**56**:1376–1381.
37. Shapovalov Y, Hoffman D, Zuch D, Bentley KLD, Elisee RA. Mitochondrial dysfunction in cancer cells due to aberrant mitochondrial replication. *J Biol Chem* 2011;**286**:22331–22338.
38. Sleigh A, Raymond-Barker P, Thackray K, et al. Mitochondrial dysfunction in patients with primary congenital insulin resistance. *J Clin Invest* 2011;**121**:2457–2461.
39. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med* 2003;**348**:2656–2668.
40. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. *Annu Rev Genet* 2005;**39**:359–407.
41. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 2004;**350**:664–671.
42. Baker BM, Haynes CM. Mitochondrial protein quality control during biogenesis and aging. *Trends Biochem Sci* 2011;**36**:254–261.
43. Onyango IG, Lu JH, Rodova M, Lezi E, Crafter AB, Swerdlow RH. Regulation of neuron mitochondrial biogenesis and relevance to brain health. *Biochim Biophys Acta* 2010;**1802**:228–234.
44. Ramalingam M, Kim S-J. Reactive oxygen/nitrogen species and their functional correlations in neurodegenerative diseases. *J Neural Transm* 2012;**119**:891–910.
45. Li S-Y, Jia Y-H, Sun W-G, et al. Stabilization of mitochondrial function by tetramethylpyrazine protects against kainate-induced oxidative lesions in the rat hippocampus. *Free Radic Biol Med* 2010;**48**:597–608.
46. Muller WE, Eckert A, Kurz C, Eckert GP, Leuner K. Mitochondrial dysfunction: Common final pathway in brain aging and alzheimer's disease-therapeutic aspects. *Mol Neurobiol* 2010;**41**:159–171.
47. Trushina E, McMurray CT. Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. *Neuroscience* 2007;**145**:1233–1248.

48. Chuang Y-C, Lin T-K, Huang H-Y, et al. Peroxisome proliferator-activated receptors γ/mitochondrial uncoupling protein 2 signaling protects against seizure-induced neuronal cell death in the hippocampus following experimental status epilepticus. *J Neuroinflammation* 2012;**9**:1–18.
49. Malinska D, Kulawiak B, Kudin AP, et al. Complex III-dependent superoxide production of brain mitochondria contributes to seizure-related ROS formation. *Biochim Biophys Acta* 2010;**1797**:1163–1170.
50. Manfredi G, Beal MF. The role of mitochondria in the pathogenesis of neurodegenerative diseases. *Brain Pathol* 2000;**10**:462–472.
51. Costa RO, Ferreiro E, Martins I, et al. Amyloid beta-induced ER stress is enhanced under mitochondrial dysfunction conditions. *Neurobiol Aging* 2012;**33**:12.
52. Hauptmann S, Scherping I, Drose S, et al. Mitochondrial dysfunction: An early event in Alzheimer pathology accumulates with age in AD transgenic mice. *Neurobiol Aging* 2009;**30**:1574–1586.
53. Gong B, Pan Y, Vempati P, et al. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. *Neurobiol Aging* 2013;**34**:1581–1588.
54. Camacho IE, Serneels L, Spittaels K, Merchiers P, Dominguez D, De Strooper B. Peroxisome proliferator-activated receptor γ induces a clearance mechanism for the amyloid-β peptide. *J Neurosci* 2004;**24**:10908–10917.
55. Folbergrová J, Ješina P, Haugvicová R, Lisý V, Houštěk J. Sustained deficiency of mitochondrial complex I activity during long periods of survival after seizures induced in immature rats by homocysteic acid. *Neurochem Int* 2010;**56**:394–403.
56. Krieger C, Duchen MR. Mitochondria, Ca(2+) and neurodegenerative disease. *Eur J Pharmacol* 2002;**447**:177–188.
57. Cronin-Furman EN, Borland MK, Bergquist KE, Bennett JP Jr, Trimmer PA. Mitochondrial quality, dynamics and functional capacity in Parkinson's disease cybrid cell lines selected for Lewy body expression. *Mol Neurodegener* 2013;**8**:1–17.
58. Imam MU, Ismail M, Ithnin H, Tubesha Z, Omar AR. Effects of germinated brown rice and its bioactive compounds on the expression of the peroxisome proliferator-activated receptor gamma gene. *Nutrients* 2013;**5**:468–477.
59. Milakovic T, Johnson GVW. Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant Huntingtin. *J Biol Chem* 2005;**280**:30773–30782.
60. Seong IS, Ivanova E, Lee JM, et al. HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. *Hum Mol Genet* 2005;**14**:2871–2880.
61. Chiang MC, Chen CM, Lee MR, et al. Modulation of energy deficiency in Huntington's disease via activation of the peroxisome proliferator-activated receptor gamma. *Hum Mol Genet* 2010;**19**:4043–4058.
62. Cui LB, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D. Transcriptional repression of PGC-alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell* 2006;**127**:59–69.
63. Fuenzalida K, Quintanilla R, Ramos P, et al. Peroxisome proliferator-activated receptor gamma up-regulates the Bcl-2 anti-apoptotic protein in neurons and induces mitochondrial stabilization and protection against oxidative stress and apoptosis. *J Biol Chem* 2007;**282**:37006–37015.
64. Da Cruz S, Parone PA, Lopes VS, et al. Elevated PGC-1 alpha activity sustains mitochondrial biogenesis and muscle function without extending survival in a mouse model of inherited ALS. *Cell Metab* 2012;**15**:778–786.
65. Bahadorani S, Mukai ST, Rabie J, Beckman JS, Phillips JP, Hilliker AJ. Expression of zinc-deficient human superoxide dismutase in Drosophila neurons produces a locomotor defect linked to mitochondrial dysfunction. *Neurobiol Aging* 2013;**34**:2322–2330.
66. Li QA, Vande Velde C, Israelson A, et al. ALS-linked mutant superoxide dismutase 1 (SOD1) alters mitochondrial protein composition and decreases protein import. *Proc Natl Acad Sci U S A* 2010;**107**:21146–21151.
67. Russell AP, Wada S, Vergani L, et al. Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis. *Neurobiol Dis* 2013;**49**:107–117.
68. Kiaei M. Peroxisome proliferator-activated receptor-gamma in amyotrophic lateral sclerosis and Huntington's disease. *PPAR Res* 2008;**8**:1–8.
69. Coussee E, De Smet P, Bogaert E, et al. G37R SOD1 mutant alters mitochondrial complex I activity, Ca2 + uptake and ATP production. *Cell Calcium* 2011;**49**:217–225.
70. Chen HC, Chan DC. Mitochondrial dynamics-fusion, fission, movement, and mitophagy-in neurodegenerative diseases. *Hum Mol Genet* 2009;**18**:R169–R176.
71. Fukui H, Moraes CT. Extended polyglutamine repeats trigger a feedback loop involving the mitochondrial complex III, the proteasome and huntingtin aggregates. *Hum Mol Genet* 2007;**16**:783–797.
72. Kilbride SM, Gluchowska SA, Telford JE, O'Sullivan C, Davey GP. High-level inhibition of mitochondrial complexes III and IV is required to increase glutamate release from the nerve terminal. *Mol Neurodegener* 2011;**6**:53.
73. Beal MF. Mitochondria take center stage in aging and neurodegeneration. *Ann Neurol* 2005;**58**:495–505.
74. Yamada ES, Respondek G, Mussner S, et al. Annonacin, a natural lipophilic mitochondrial complex I inhibitor, increases phosphorylation of tau in the brain of EDP-17 transgenic mice. *Exp Neurol* 2014;**253**:113–125.
75. Hoglinger GU, Carrard G, Michel PP, et al. Dysfunction of mitochondrial complex I and the proteasome: Interactions between two biochemical deficits in a cellular model of Parkinson's disease. *J Neurochem* 2003;**86**:1297–1307.
76. Menzies FM, Cookson MR, Taylor RW, et al. Mitochondrial dysfunction in a cell culture model of familial amyotrophic lateral sclerosis. *Brain* 2002;**125**:1522–1533.
77. Benit P, Slama A, Cartault F, et al. Mutant NDUFS3 subunit of mitochondrial complex I causes Leigh syndrome. *J Med Genet* 2004;**41**:14–17.
78. Andreazza AC, Shao L, Wang JF, Young LT. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch Gen Psychiatry* 2010;**67**:360–368.
79. Chretien D, Bénit P, Chol M, et al. Assay of mitochondrial respiratory chain complex I in human lymphocytes and cultured skin fibroblasts. *Biochem Biophys Res Commun* 2003;**301**:222–224.
80. Quinlan CL, Orr AL, Perevoshchikova IV, Treberg JR, Ackrell BA, Brand MD. Mitochondrial complex II can generate reactive oxygen species at high rates in both the forward and reverse reactions. *J Biol Chem* 2012;**287**:27255–27264.
81. Ganesh J, Wong L-JC, Gorman EB. Mitochondrial respiratory chain complex II. In: Wong L-JC, editor. *Mitochondrial disorders caused by nuclear genes*. New York: Springer, 2013;203–218.
82. Dröse S. Differential effects of complex II on mitochondrial ROS production and their relation to cardioprotective pre- and postconditioning. *Biochim Biophys Acta* 2013;**1827**:578–587.
83. Haut S, Brivet M, Touati G, et al. A deletion in the human QP-C gene causes a complex III deficiency resulting in hypoglycaemia and lactic acidosis. *Hum Genet* 2003;**113**:118–122.
84. Borisov VB. Defects in mitochondrial respiratory complexes III and IV, and human pathologies. *Mol Aspects Med* 2002;**23**:385–412.
85. Diaz F, Fukui H, Garcia S, Moraes CT. Cytochrome c oxidase is required for the assembly/stability of respiratory complex I in mouse fibroblasts. *Mol Cell Biol* 2006;**26**:4872–4881.
86. Li X, Yang Y. Mitochondrial disorders associated with mitochondrial respiratory chain complex V deficiency. *Zhongguo Dang Dai Er Ke Za Zhi* 2013;**15**:596–600.
87. Jonckheere AI, Smeitink JA, Rodenburg RJ. Mitochondrial ATP synthase: Architecture, function and pathology. *J Inherit Metab Dis* 2012;**35**:211–225.
88. Valerio A, Bertolotti P, Delbarba A, et al. Glycogen synthase kinase-3 inhibition reduces ischemic cerebral damage, restores impaired mitochondrial biogenesis and prevents ROS production. *J Neurochem* 2011;**116**:1148–1159.
89. Golpich M, Rahmani B, Ibrahim NM, et al. Preconditioning as a potential strategy for the prevention of Parkinson's disease. *Mol Neurobiol* 2015;**51**:313–330.
90. Rosenstock TR, Rego AC. Modified mitochondrial dynamics, turnover and function in neurodegeneration: A focus on Huntington's Disease. In: Lou P-H, Petersen N, editors. *Cell Bioener Health Dis: New Perspectives in Mitochondrial Biology*. Kerala: *Research Signpost*; 2012;149–194.
91. Zhang Q, Wu Y, Zhang P, et al. Exercise induces mitochondrial biogenesis after brain ischemia in rats. *Neuroscience* 2012;**205**:10–17.
92. Uittenbogaard M, Chiaramello A. Mitochondrial biogenesis: A therapeutic target for neurodevelopmental disorders and neurodegenerative diseases. *Curr Pharm Des* 2014;**20**:5574–5593.
93. Dominy JE, Puigserver P. Mitochondrial biogenesis through activation of nuclear signaling proteins. *Cold Spring Harbor Perspect Biol* 2013;**5**:1–18.
94. Scarpulla RC. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol Rev* 2008;**88**:611–638.
95. Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, Murphy E. Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. *Circ Res* 2010;**106**:1681–U46.
96. Vercauteren K, Pasko RA, Gleyzer N, Marino VM, Scarpulla RC. PGC-1-related coactivator: Immediate early expression and characterization of a CREB/NRF-1 binding domain associated with cytochrome c promoter occupancy and respiratory growth. *Mol Cell Biol* 2006;**26**:7409–7419.
97. Wu ZD, Huang XM, Feng YJ, et al. Transducer of regulated CREB-binding proteins (TORCs) induce PGC-1 alpha transcription and mitochondrial biogenesis in muscle cells. *Proc Natl Acad Sci U S A* 2006;**103**:14379–14384.
98. Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim Biophys Acta* 2011;**1813**:1269–1278.
99. Yin W, Signore AP, Iwai M, Cao GD, Gao YQ, Chen J. Rapidly increased neuronal mitochondrial biogenesis after hypoxic-ischemic brain injury. *Stroke* 2008;**39**:3057–3063.
100. Chen YC, Wu JS, Tsai HD, et al. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and neurodegenerative disorders. *Mol Neurobiol* 2012;**46**:114–124.
101. Canto C, Gerhart-Hines Z, Feige JN, et al. AMPK regulates energy expenditure by modulating NAD(+) metabolism and SIRT1 activity. *Nature* 2009;**458**:1056–U140.

102. Steinberg GR, Kemp BE. AMPK in Health and Disease. *Physiol Rev* 2009;**89**:1025–1078.
103. Hardie DG. The AMP-activated protein kinase pathway – new players upstream and downstream. *J Cell Sci* 2004;**117**:5479–5487.
104. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. *J Pharmacol Exp Ther* 2012;**342**:619–630.
105. Reznick RM, Shulman GI. The role of AMP-activated protein kinase in mitochondrial biogenesis. *J Physiol* 2006;**574**:33–39.
106. Lee H-L, Chen C-L, Yeh ST, Zweier JL, Chen Y-R. Biphasic modulation of the mitochondrial electron transport chain in myocardial ischemia and reperfusion. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1410–H1422.
107. Fingar DC, Blenis J. Target of rapamycin (TOR): An integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. *Oncogene* 2004;**23**:3151–3171.
108. Li Y, Corradetti MN, Inoki K, Guan KL. TSC2: Filling the GAP in the mTOR signaling pathway. *Trends Biochem Sci* 2004;**29**:32–38.
109. Piantadosi CA, Suliman HB. Mitochondrial transcription factor A induction by redox activation of nuclear respiratory factor 1. *J Biol Chem* 2006;**281**:324–333.
110. Min S-W, Sohn PD, Cho S-H, Swanson RA, Gan L. Sirtuins in neurodegenerative diseases: An update on potential mechanisms. *Front Aging Neurosci* 2013;**5**:1–9.
111. Herskovits AZ, Guarente L. Sirtuin deacetylases in neurodegenerative diseases of aging. *Cell Res* 2013;**23**:746–758.
112. Kanfi Y, Naiman S, Amir G, et al. The sirtuin SIRT6 regulates lifespan in male mice. *Nature* 2012;**483**:218–221.
113. Kong X, Wang R, Xue Y, et al. Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PLoS One* 2010;**5**: e11707.
114. Schreiber SN, Emter R, Hock MB, et al. The estrogen-related receptor alpha (ERR alpha) functions in PPAR gamma coactivator 1 alpha (PGC-1 alpha)-induced mitochondrial biogenesis. *Proc Natl Acad Sci U S A* 2004;**101**:6472–6477.
115. Handschin C, Spiegelman BM. Peroxisome proliferator-activated receptor γ coactivator 1 coactivators, energy homeostasis, and metabolism. *Endocr Rev* 2006;**27**:728–735.
116. Madrazo JA, Kelly DP. The PPAR trio: Regulators of myocardial energy metabolism in health and disease. *J Mol Cell Cardiol* 2008;**44**:968–975.
117. Andersen G, Wegner L, Yanagisawa K, et al. Evidence of an association between genetic variation of the coactivator PGC-1 beta and obesity. *J Med Genet* 2005;**42**:402–407.
118. Dang CV, Li F, Lee LA. Could MYC induction of mitochondrial biogenesis be linked to ROS production and genomic instability? *Cell Cycle* 2005;**4**:1465–1466.
119. Ramachandran B, Yu GS, Gulick T. Nuclear respiratory factor 1 controls myocyte enhancer factor 2A transcription to provide a mechanism for coordinate expression of respiratory chain subunits. *J Biol Chem* 2008;**283**:11935–11946.
120. Rocha M, Hernandez-Mijares A, Garcia-Malpartida K, Bañuls C, Bellod L, M Victor V. Mitochondria-targeted antioxidant peptides. *Curr Pharm Des* 2010;**16**:3124–3131.
121. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol* 2014;**171**:2029–2050.
122. Petri S, Kiaei M, Damiano M, et al. Cell-permeable peptide antioxidants as a novel therapeutic approach in a mouse model of amyotrophic lateral sclerosis. *J Neurochem* 2006;**98**:1141–1148.
123. Murphy MP, Smith RA. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu Rev Pharmacol Toxicol* 2007;**47**:629–656.
124. Cochemé HM, Kelso GF, James AM, et al. Mitochondrial targeting of quinones: Therapeutic implications. *Mitochondrion* 2007;**7**:S94–S102.
125. Dumont M, Kipiani K, Yu F, et al. Coenzyme Q10 decreases amyloid pathology and improves behavior in a transgenic mouse model of Alzheimer's disease. *J Alzheimers Dis* 2011;**27**:211–223.
126. Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: Preclinical and clinical outcomes. *Biochim Biophys Acta* 2014;**1842**:1282–1294.
127. Yang L, Calingasan NY, Wille EJ, et al. Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases. *J Neurochem* 2009;**109**:1427–1439.
128. Miquel E, Cassina A, Martínez-Palma L, et al. Neuroprotective effects of the mitochondria-targeted antioxidant MitoQ in a model of inherited amyotrophic lateral sclerosis. *Free Radic Biol Med* 2014;**70**:204–213.
129. Hou Y, Li S, Wu M, et al. Mitochondria-targeted peptide SS-31 attenuates renal injury via an antioxidant effect in diabetic nephropathy. *Am J Physiol Renal Physiol* 2016;**310**:F547–F559.
130. Cho S, Szeto HH, Kim E, Kim H, Tolhurst AT, Pinto JT. A novel cell-permeable antioxidant peptide, SS31, attenuates ischemic brain injury by down-regulating CD36. *J Biol Chem* 2007;**282**:4634–4642.
131. Szeto HH. *Cell-permeable, mitochondrial-targeted, peptide antioxidants*. Drug addiction. New York: Springer, 2008;535–546.
132. Manczak M, Mao P, Calkins MJ, et al. Mitochondria-targeted antioxidants protect against amyloid-β toxicity in Alzheimer's disease neurons. *J Alzheimers Dis* 2010;**20** (S2):609–631.
133. Yang L, Zhao K, Calingasan NY, Luo G, Szeto HH, Beal MF. Mitochondria targeted peptides protect against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine neurotoxicity. *Antioxid Redox Signal* 2009;**11**:2095–2104.
134. Chandra A, Johri A, Beal MF. Prospects for neuroprotective therapies in prodromal Huntington's disease. *Mov Disord* 2014;**29**:285–293.
135. Nussbaum JM, Schilling S, Cynis H, et al. Prion-like behaviour and tau-dependent cytotoxicity of pyroglutamylated amyloid-beta. *Nature* 2012;**485**:651–655.
136. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 2013;**493**: 674–678.
137. Israel MA, Yuan SH, Bardy C, et al. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature* 2012;**482**:216–U107.
138. Dragicevic N, Mamcarz M, Zhu YY, et al. Mitochondrial amyloid-beta levels are associated with the extent of mitochondrial dysfunction in different brain regions and the degree of cognitive impairment in alzheimer's transgenic mice. *J Alzheimers Dis* 2010;**20**:S535–S550.
139. Zhang H, Jia H, Liu J, et al. Combined R-α–lipoic acid and acetyl-L-carnitine exerts efficient preventative effects in a cellular model of Parkinson's disease. *J Cell Mol Med* 2010;**14**:215–225.
140. Marongiu R, Spencer B, Crews L, et al. Mutant Pink1 induces mitochondrial dysfunction in a neuronal cell model of Parkinson's disease by disturbing calcium flux. *J Neurochem* 2009;**108**:1561–1574.
141. Eckert A, Nisbet R, Grimm A, Götz J. March separate, strike together—Role of phosphorylated TAU in mitochondrial dysfunction in Alzheimer's disease. *Biochim Biophys Acta* 2014;**1842**:1258–1266.
142. Hroudová J, Singh N, Fišar Z. Mitochondrial dysfunctions in neurodegenerative diseases: Relevance to Alzheimer's disease. *BioMed Res Int* 2014;**2014**:1–9.
143. Zhang L, Zhang S, Maezawa I, et al. Modulation of mitochondrial complex I activity averts cognitive decline in multiple animal models of familial Alzheimer's disease. *EBioMedicine* 2015;**2**:294–305.
144. Kruger J, Hinttala R, Majamaa K, Remes AM. Mitochondrial DNA haplogroups in early-onset Alzheimer's disease and frontotemporal lobar degeneration. *Mol Neurodegener* 2010;**5**:6.
145. Manczak M, Jung YS, Park BS, Partovi D, Reddy PH. Time-course of mitochondrial gene expressions in mice brains: Implications for mitochondrial dysfunction, oxidative damage, and cytochrome c in aging. *J Neurochem* 2005;**92**:494–504.
146. Liang WS, Reiman EM, Valla J, et al. Alzheimer's disease is associated with reduced expression of energy in posterior cingulate metabolism genes neurons. *Proc Natl Acad Sci U S A* 2008;**105**:4441–4446.
147. Diana A, Simic G, Sinforiani E, Orru N, Pichiri G, Bono G. Mitochondria morphology and DNA content upon sublethal exposure to beta-amyloid(1-42) peptide. *Coll Anthropol* 2008;**32**:51–58.
148. Puranam KL, Wu GH, Strittmatter WJ, Burke JR. Polyglutamine expansion inhibits respiration by increasing reactive oxygen species in isolated mitochondria. *Biochem Biophys Res Commun* 2006;**341**:607–613.
149. Liu Z, Li P, Wu J, et al. The cascade of oxidative stress and tau protein autophagic dysfunction in Alzheimer's disease. In: Zerr I, editor. *Alzheimer's Disease - Challenges for the Future*. Rijeka: *Intech*, 2015.
150. Zhang Q, Yu JT, Wang P, et al. Mitochondrial transcription factor A (TFAM) polymorphisms and risk of late-onset Alzheimer's disease in Han Chinese. *Brain Res* 2011;**1368**:355–360.
151. Blacker D, Bertram L, Saunders AJ, et al. Results of a high-resolution genome screen of 437 Alzheimer's Disease families. *Hum Mol Genet* 2003;**12**:23–32.
152. Gunther C, von Hadeln K, Muller-Thomsen T, et al. Possible association of mitochondrial transcription factor A (TFAM) genotype with sporadic Alzheimer disease. *Neurosci Lett* 2004;**369**:219–223.
153. d'Abramo C, Ricciarelli R, Pronzato MA, Davies P. Troglitazone, a peroxisome proliferator-activated receptor-γ agonist, decreases tau phosphorylation in CHOtau4R cells. *J Neurochem* 2006;**98**:1068–1077.
154. Du L-L, Chai D-M, Zhao L-N, et al. AMPK activation ameliorates Alzheimer's disease-like pathology and spatial memory impairment in a streptozotocin-induced Alzheimer's disease model in rats. *J Alzheimers Dis* 2015;**43**:775–784.
155. Kim D, Nguyen MD, Dobbin MM, et al. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. *EMBO J* 2007;**26**:3169–3179.
156. Tomiyama H, Mizuta I, Li Y, et al. LRRK2 P755L variant in sporadic Parkinson's disease. *J Hum Genet* 2008;**53**:1012–1015.
157. Tomas-Camardiel M, Rite I, Herrera AJ, et al. Minocycline reduces the lipopolysaccharide-induced inflammatory reaction, peroxynitrite-mediated nitration of proteins, disruption of the blood-brain barrier, and damage in the nigral dopaminergic system. *Neurobiol Dis* 2004;**16**:190–201.
158. Korecka JA, Eggers R, Swaab DF, Bossers K, Verhaagen J. Modeling early Parkinson's disease pathology with chronic low dose MPTP treatment. *Restor Neurol Neurosci* 2013;**31**:155–167.
159. Greenamyre JT, Hastings TG. Parkinson's: Divergent causes, convergent mechanisms. *Science* 2004;**304**:1120–1122.
160. Ortega-Arellano HF, Jimenez-Del-Rio M, Velez-Pardo C. Life span and locomotor activity modification by glucose and polyphenols in Drosophila melanogaster chronically exposed to oxidative stress-stimuli: Implications in Parkinson's disease. *Neurochem Res* 2011;**36**:1073–1086.

161. Weise J, Engelhorn T, Dörfler A, Aker S, Bähr M, Hufnagel A. Expression time course and spatial distribution of activated caspase-3 after experimental status epilepticus: Contribution of delayed neuronal cell death to seizure-induced neuronal injury. *Neurobiol Dis* 2005;**18**:582–590.
162. Ng C-H, Guan MS, Koh C, et al. AMP kinase activation mitigates dopaminergic dysfunction and mitochondrial abnormalities in Drosophila models of Parkinson's disease. *J Neurosci* 2012;**32**:14311–14317.
163. Choi HJ, Lee SY, Cho Y, No H, Kim SW, Hwang O. Tetrahydrobiopterin causes mitochondrial dysfunction in dopaminergic cells: Implications for Parkinson's disease. *Neurochem Int* 2006;**48**:255–262.
164. Keeney PM, Xie J, Capaldi RA, Bennett JP. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. *J Neurosci* 2006;**26**: 5256–5264.
165. Tobon-Velasco JC, Limon-Pacheco JH, Orozco-Ibarra M, et al. 6-OHDA-induced apoptosis and mitochondrial dysfunction are mediated by early modulation of intracellular signals and interaction of Nrf2 and NF-kappa B factors. *Toxicology* 2013;**304**:109–119.
166. Cho D-H, Nakamura T, Lipton SA. Mitochondrial dynamics in cell death and neurodegeneration. *Cell Mol Life Sci* 2010;**67**:3435–3447.
167. Abou-Sleiman PM, Muqit MMK, Wood NW. Expanding insights of mitochondrial dysfunction in Parkinson's disease. *Nat Rev Neurosci* 2006;**7**:207–219.
168. Sherer TB, Betarbet R, Stout AK, et al. An in vitro model of Parkinson's disease: Linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. *J Neurosci* 2002;**22**:7006–7015.
169. Shamoto-Nagai M, Maruyama W, Kato Y, et al. An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells. *J Neurosci Res* 2003;**74**:589–597.
170. Nakamura T, Cho DH, Lipton SA. Redox regulation of protein misfolding, mitochondrial dysfunction, synaptic damage, and cell death in neurodegenerative diseases. *Exp Neurol* 2012;**238**:12–21.
171. Thomas RR, Keeney PM, Bennett JP. Impaired complex-I mitochondrial biogenesis in Parkinson disease frontal cortex. *J Parkinsons Dis* 2012;**2**:67–76.
172. Schon EA, Przedborski S. Mitochondria: The next (Neurode)generation. *Neuron* 2011;**70**:1033–1053.
173. Zhu JH, Gusdon AM, Cimen H, Van Houten B, Koc E, Chu CT. Impaired mitochondrial biogenesis contributes to depletion of functional mitochondria in chronic MPP+ toxicity: Dual roles for ERK1/2. *Cell Death Dis* 2012;**3**:10.
174. Zheng B, Liao ZX, Locascio JJ, et al. PGC-1 alpha, a potential therapeutic target for early intervention in Parkinson's disease. *Sci Transl Med* 2010;**2**:14.
175. Chu CT. A pivotal role for PINK1 and autophagy in mitochondrial quality control: Implications for Parkinson disease. *Hum Mol Genet* 2010;**19**:R28–R37.
176. Schmidt S, Linnartz B, Mendritzki S, et al. Genetic mouse models for Parkinson's disease display severe pathology in glial cell mitochondria. *Hum Mol Genet* 2011;**20**:1197–1211.
177. Kuroda Y, Mitsui T, Kunishige M, et al. Parkin enhances mitochondrial biogenesis in proliferating cells. *Hum Mol Genet* 2006;**15**:883–895.
178. Pilsl A, Winklhofer KF. Parkin, PINK1 and mitochondrial integrity: Emerging concepts of mitochondrial dysfunction in Parkinson's disease. *Acta Neuropathol* 2012;**123**:173–188.
179. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: Molecular mechanisms and pathophysiological consequences. *EMBO J* 2012;**31**:3038–3062.
180. Dagda RK, Pien I, Wang R, et al. Beyond the mitochondrion: Cytosolic PINK1 remodels dendrites through Protein Kinase A. *J Neurochem* 2014;**128**:864–877.
181. Narendra DP, Jin SM, Tanaka A, et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol* 2010;**8**:e1000298.
182. Lazarou M, Narendra DP, Jin SM, Tekle E, Banerjee S, Youle RJ. PINK1 drives Parkin self-association and HECT-like E3 activity upstream of mitochondrial binding. *J Cell Biol* 2013;**200**:163–172.
183. Gegg ME, Cooper JM, Schapira AH, Taanman J-W. Silencing of PINK1 expression affects mitochondrial DNA and oxidative phosphorylation in dopaminergic cells. *PLoS One* 2009;**4**:e4756.
184. Dinkova-Kostova AT, Abramov AY. The emerging role of Nrf2 in mitochondrial function. *Free Radic Biol Med* 2015;**88**:179–188.
185. Lin T-K, Liou C-W, Chen S-D, et al. Mitochondrial dysfunction and biogenesis in the pathogenesis of Parkinson's disease. *Chang Gung Med J* 2009;**32**:589–599.
186. Gaweda-Walerych K, Safranow K, Maruszak A, et al. Mitochondrial transcription factor A variants and the risk of Parkinson's disease. *Neurosci Lett* 2010;**469**:24–29.
187. Keeney PM, Quigley CK, Dunham LD, et al. Mitochondrial gene therapy augments mitochondrial physiology in a Parkinson's disease cell model. *Hum Gene Ther* 2009;**20**:897–907.
188. Breidert T, Callebert J, Heneka MT, Landreth G, Launay JM, Hirsch EC. Protective action of the peroxisome proliferator-activated receptor-gamma agonist pioglitazone in a mouse model of Parkinson's disease. *J Neurochem* 2002;**82**:615–624.
189. Heneka MT, Landreth GE, Hull M. Drug Insight: Effects mediated by peroxisome proliferator-activated receptor-gamma in CNS disorders. *Nat Clin Pract Neurol* 2007;**3**:496–504.
190. Martin HL, Mounsey RB, Mustafa S, Sathe K, Teismann P. Pharmacological manipulation of peroxisome proliferator-activated receptor gamma (PPAR gamma) reveals a role for anti-oxidant protection in a model of Parkinson's disease. *Exp Neurol* 2012;**235**:528–538.
191. Hang L, Basil AH, Lim K-L. Nutraceuticals in Parkinson's Disease. *NeuroMol Med* 2016;**18**:306–321.
192. Donmez G, Arun A, Chung C-Y, McLean PJ, Lindquist S, Guarente L. SIRT1 protects against α-synuclein aggregation by activating molecular chaperones. *J Neurosci* 2012;**32**:124–132.
193. Bennett EJ, Shaler TA, Woodman B, et al. Global changes to the ubiquitin system in Huntington's disease. *Nature* 2007;**448**:704–708.
194. Yang SH, Cheng PH, Banta H, et al. Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* 2008;**453**:921–U56.
195. Quintanilla RA, Jin YN, Fuenzalida K, Bronfman M, Johnson GV. Rosiglitazone treatment prevents mitochondrial dysfunction in mutant Huntingtin-expressing cells possible role of peroxisome proliferator-activated receptor-γ (PPARγ) in the pathogenesis of Huntington disease. *J Biol Chem* 2008;**283**:25628–25637.
196. Chiang M-C, Chern Y, Juo C-G. The dysfunction of hepatic transcriptional factors in mice with Huntington's Disease. *Biochim Biophys Acta* 2011;**1812**:1111–1120.
197. Chaturvedi RK, Calingasan NY, Yang L, Hennessey T, Johri A, Beal MF. Impairment of PGC-1alpha expression, neuropathology and hepatic steatosis in a transgenic mouse model of Huntington's disease following chronic energy deprivation. *Hum Mol Genet* 2010;**19**:3190–3205.
198. Chaturvedi RK, Adhihetty P, Shukla S, et al. Impaired PGC-1α function in muscle in Huntington's disease. *Hum Mol Genet* 2009;**18**:3048–3065.
199. Phan J, Hickey MA, Zhang PX, Chesselet MF, Reue K. Adipose tissue dysfunction tracks disease progression in two Huntington's disease mouse models. *Hum Mol Genet* 2009;**18**:1006–1016.
200. Weydt P, Pineda VV, Torrence AE, et al. Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1α in Huntington's disease neurodegeneration. *Cell Metab* 2006;**4**:349–362.
201. Chiang M-C, Chern Y, Huang R-N. PPARgamma rescue of the mitochondrial dysfunction in Huntington's disease. *Neurobiol Dis* 2012;**45**:322–328.
202. Reddy PH, Mao P, Manczak M. Mitochondrial structural and functional dynamics in Huntington's disease. *Brain Res Rev* 2009;**61**:33–48.
203. Pandey M, Varghese M, Sindhu KM, et al. Mitochondrial NAD+-linked State 3 respiration and complex-I activity are compromised in the cerebral cortex of 3-nitropropionic acid-induced rat model of Huntington's disease. *J Neurochem* 2008;**104**:420–434.
204. Kim J, Moody JP, Edgerly CK, et al. Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. *Hum Mol Genet* 2010;**19**:3919–3935.
205. Benit P, Lebon S, Rustin P. Respiratory-chain diseases related to complex III deficiency. *Biochim Biophys Acta* 2009;**1793**:181–185.
206. Knott AB, Perkins G, Schwarzenbacher R, Bossy-Wetzel E. Mitochondrial fragmentation in neurodegeneration. *Nat Rev Neurosci* 2008;**9**:505–518.
207. Johri A, Chandra A, Beal MF. PGC-1 alpha, mitochondrial dysfunction, and Huntington's disease. *Free Radic Biol Med* 2013;**62**:37–46.
208. Johri A, Calingasan NY, Hennessey TM, et al. Pharmacologic activation of mitochondrial biogenesis exerts widespread beneficial effects in a transgenic mouse model of Huntington's disease. *Hum Mol Genet* 2012;**21**:1124–1137.
209. Tsunemi T, Ashe TD, Morrison BE, et al. PGC-1 alpha rescues huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. *Sci Transl Med* 2012;**4**:142–197.
210. Bastin J, Aubey F, Rotig A, Munnich A, Djouadi F. Activation of peroxisome proliferator-activated receptor pathway stimulates the mitochondrial respiratory chain and can correct deficiencies in patients' cells lacking its components. *J Clin Endocrinol Metab* 2008;**93**:1433–1441.
211. Wenz TN, Wang X, Marini M, Moraes CT. A metabolic shift induced by a PPAR panagonist markedly reduces the effects of pathogenic mitochondrial tRNA mutations. *J Cell Mol Med* 2011;**15**:2317–2325.
212. Jiang M, Wang J, Fu J, et al. Neuroprotective role of Sirt1 in mammalian models of Huntington's disease through activation of multiple Sirt1 targets. *Nat Med* 2012;**18**:153–158.
213. Jung C, Higgins CM, Xu Z. Mitochondrial electron transport chain complex dysfunction in a transgenic mouse model for amyotrophic lateral sclerosis. *J Neurochem* 2002;**83**:535–545.
214. Duffy LM, Chapman AL, Shaw PJ, Grierson AJ. Review: The role of mitochondria in the pathogenesis of amyotrophic lateral sclerosis. *Neuropathol Appl Neurobiol* 2011;**37**:336–352.
215. Lee J, Kannagi M, Ferrante RJ, Kowall NW, Ryu H. Activation of Ets-2 by oxidative stress induces Bcl-xL expression and accounts for glial survival in amyotrophic lateral sclerosis. *FASEB J* 2009;**23**:1739–1749.
216. Benedusi V, Martorana F, Brambilla L, Maggi A, Rossi D. The Peroxisome Proliferator-Activated Receptor γ (PPARγ) controls natural protective mechanisms against lipid peroxidation in Amyotrophic Lateral Sclerosis. *J Biol Chem* 2012;**287**:35899–35911.
217. Perera ND, Sheean RK, Scott JW, Kemp BE, Horne MK, Turner BJ. Mutant TDP-43 deregulates AMPK activation by PP2A in ALS models. *PLoS One* 2014;**9**:e90449.