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REVIEW

Role of PGC-1α in Mitochondrial Quality Control in Neurodegenerative Diseases

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Abstract

As one of the major cell organelles responsible for ATP production, it is important that neurons maintain mitochondria with structural and functional integrity; this is especially true for neurons with high metabolic requirements. When mitochondrial damage occurs, mitochondria are able to maintain a steady state of functioning through molecular and organellar quality control, thus ensuring neuronal function. And when mitochondrial quality control (MQC) fails, mitochondria mediate apoptosis. An apparently key molecule in MQC is the transcriptional coactivator peroxisome proliferator activated receptor γ coactivator-1α (PGC-1α). Recent findings have demonstrated that upregulation of PGC-1α expression in neurons can modulate MQC to prevent mitochondrial dysfunction in certain in vivo and in vitro aging or neurodegenerative encephalopathy models, such as Huntington's disease, Alzheimer's disease, and Parkinson's disease. Because mitochondrial function and quality control disorders are the basis of pathogenesis in almost all neurodegenerative diseases (NDDs), the role of PGC-1α may make it a viable entry point for the treatment of such diseases. This review focuses on multi-level MQC in neurons, as well as the regulation of MQC by PGC-1α in these major NDDs.

Keywords Peroxisome proliferator activated receptor γ coactivator-1α · Mitochondrial quality control · Signaling pathway · Neurodegenerative diseases · Neuroprotective effects

Introduction

Under normal physiological conditions, the number, morphology, and function of mitochondria remain relatively stable. This is due to multiple mitochondrial quality control (MQC) processes that operate at various scales, ranging from the degradation of proteins by mitochondrial proteases to the degradation of selected entire organelles in lysosomes. We summarized them into the following aspects: mitochondrial unfolded protein response (mtUPR) at the molecular level, mitochondrial fission, fusion and mitophagy at the organelle level, as well as newly discovered mitochondria-derived vesicles (MDVs) and mitochondrial spheroids. When MQC fails and the mitochondria are unable to perform their vital functions, the cells undergo mitochondria-mediated apoptosis. Neurodegenerative diseases (NDDs) can lead to structural and functional deterioration of nerve tissue and irreversible damage [1]. In the past 30 years, many studies have convincingly linked mitochondrial dysfunction to NDDs [2], and current research into NDDs strongly suggests that these diseases are associated with MQC defects.

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Peroxisome proliferator activated receptor γ (PPARγ) coactivator-1α (PGC-1α) is a transcriptional coactivator. Previous studies have focused on the role of PGC-1α in dealing with oxidative stress, and how PGC-1α exerts neuroprotective effects by participating in the regulation of mitochondrial energy metabolism and biogenesis [3, 4]. Few studies have investigated PGC-1α-mediated neuroprotection in MQC. However, there are reports that activation of the PGC-1α signaling pathway can indeed participate in MQC regulation and reduce neuronal damage. This review focuses on the regulation of this coactivator in MQC in NDDs. PGC-1α is expected to serve as a novel entry point for the treatment of these degenerative diseases.

MQC in Neurons

To a large extent, the neural cell population relies on correct mitochondrial function, which in turn is closely related to mitochondrial quality. Under normal physiological conditions, mitochondria can limit and delay the accumulation and increase of abnormal mitochondrial changes. Mitochondria achieve this via the actions of related proteins and enzymes, as well as through mitochondrial fission, fusion, mitophagy, MDVs, mitochondrial spheroids, and so on. In this way, mitochondria ensure the continuation of their normal functions, and this process is known as MQC [5]. The maintenance of cellular and organismal homeostasis can therefore be said to depend on MQC [6].

At the molecular level, mitochondria achieve quality control through mitochondrial unfolded protein response (mtUPR). mtUPR is an adaptive transcriptional response during mitochondrial dysfunction that promotes recovery of the mitochondrial network and survival of the cell [7]. The mtUPR can be activated by conditions that cause mitochondrial stress, such as depletion of mitochondrial DNA (mtDNA), OXPHOS components, mitochondrial proteases, perturbation of mitochondrial ribosomes, or exposure to ROS [8]. ROS produced by mitochondria induce protein damage, unfolding, misfolding, and aggregation [9]. When misfolded proteins accumulate in mitochondria, mitochondria respond adaptively by enhancing chaperone and protease activity, among other responses, to refold or degrade these proteins [10]. In higher eukaryotes, proteins that are destroyed or unfolded in the mitochondrial matrix are degraded by Lon protease. For example, in studies of spinal motor neurons in amyotrophic lateral sclerosis (ALS), Lon protease is involved in the degradation of damaged proteins such as aconitase and ATP synthase, which are caused by SOD1 mutations [11]. In addition, Lon protease maintains normal mitochondrial transcription levels by degrading excess mitochondrial transcription factor A (TFAM) [12], and this reduces the damage to mitochondrial function that may result from high mtDNA copies [13]. Lon protease also maintains the stability of the chaperone by binding to molecular chaperones such as the Hsp60-mtHsp70 complex [14]. This delays motor neuron apoptosis caused by mitochondrial dysfunction.

At the organellar level, MQC reduces mitochondrial damage by fission and fusion [15]. ROS induces mitochondrial fission, leading to fragmentation of mitochondria [16]. These fragmented mitochondria have a lower membrane potential, produce less ATP and more ROS, and promote the release of pro-apoptotic mitochondrial proteins. Mitochondria reverse this fragmentation using fusion [16]. Mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (Opa1) mediate fusion of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), respectively [17, 18] (Fig. 1). Prohibitins are ubiquitous, evolutionarily conserved proteins that are mainly localized in IMM. The mitochondrial prohibitin complex comprises two subunits, PHB1 and PHB2 [19]. PHB complexes preserve mitochondrial fusion and the tubular morphology of the mitochondrial network [20]. Active mitochondrial fusion is important not only to maintain mitochondrial integrity and to reduce mitochondrial ROS production, but also to activate mtDNA replication elevating mtDNA copy number [16]. Mitochondrial fusion also allows the renewal of mitochondria and remodels mitochondrial cristae shape, which directly affects the stability of the electron transport chain (ETC) complex, and especially complex IV [21]. When mitochondrial function is deficient, dynamin-related protein 1 (Drp1)- and mitochondrial fission 1 protein (Fis1)-mediated fission can be promoted [22]. Drp1 is a GTPase protein localized to the cytoplasm, and it has multiple phosphorylation sites, including Ser600, Ser616 and so on [23, 24]. It is recruited to the OMM receptor Fis1 after calmodulin-dependent protein kinase-mediated phosphorylation [25]. Phosphorylated Drp1 oligomerizes and shrinks to form a split-loop structure, and the mitochondria then begins to divide [26]. Mitochondrial fission helps to isolate damaged mitochondrial segments, thereby promoting mitophagy, and fusion helps to inhibit apoptotic programs reliant on mitochondrial fission and cristae remodelling [27]. Normal mitochondrial function in neurons is therefore maintained by mitochondrial fission and fusion.

At the organelle level, mitochondria also selectively degrade defective mitochondria through mitophagy to maintain mitochondrial function and integrity [28, 29]. Mitophagy is closely associated with NDDs [30]. At present, the known mechanism for the regulation of mitophagy is as follows: Parkin is a cytosolic E3 ubiquitin ligase, and PTEN-induced kinase 1 (PINK1) is a mitochondrial Ser/Thr protein kinase, and both are involved in mitophagy [31]. Under basal conditions, PINK1 is imported into mitochondria in a manner dependent on the multiprotein TOM and

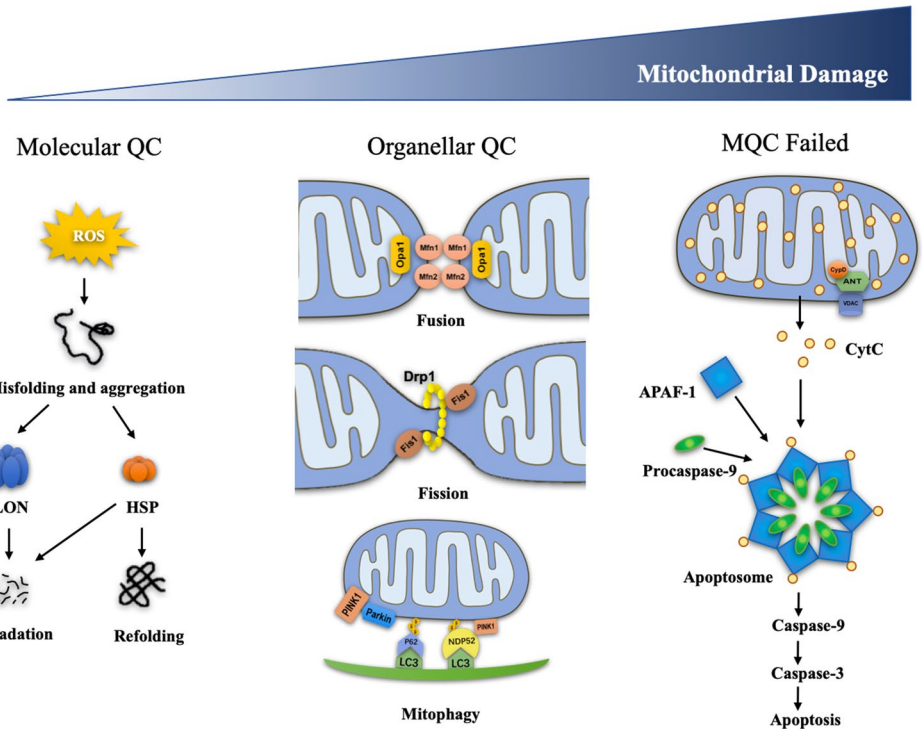

Fig. 1 Mitochondrial damage evolution and mitochondrial quality control. **a** *Molecular quality control* (*QC*): mitochondria can refold or degrade misfolded and aggregated proteins caused by ROS by enhancing chaperone and Lon protease activity. (**b**) *Organellar QC*: mitochondria reduce damaged mitochondria by fission, fusion, and mitophagy. (**c**) *MQC failed*: extensive mitochondrial damage leads to apoptosis

TIM complexes. PINK1 undergoes proteolytic cleavage by the matrix protein MPP and by the IMM protein PARL [32]. Processed PINK1 is then targeted to the proteasome for degradation [33]. Upon mitochondrial stress or damage accompanied by membrane depolarization, PINK1 import is compromised. PINK1 therefore cannot be processed by PARL and is stabilized on the OMM, where it phosphorylates both Parkin and ubiquitin [34]. PINK1 can autophosphorylate itself, and activated p-PINK1 in turn leads to the phosphorylation of Parkin and its subsequent localization on the OMM [35]. The OMM protein is then ubiquitinated and thus recognized by p62 to bind to the autophagy-related protein light chain 3 (LC3)-II to form autophagosomes, which thereby induces mitophagy [36] (Fig. 1). Therefore, through the combined activity of PINK1 and Parkin, dysfunctional mitochondria are selectively removed by mitophagy, thus removing the cell's primary source of ROS and avoiding their damaging effects [31]. Parkin/PINK1 mitophagy pathway is not responsible for all the mitophagy processes, such as receptor-mediated mitophagy. BNIP3 (BCL2/adenovirus E1B 19-kDa interacting protein 3), NIX/BNIP3L (BCL2/adenovirus E1B 19 kDa interacting protein 3 like), FUNDC1 are OMM receptors containing an LC3-interacting region that directly binds to LC3 proteins allowing the recruitment of the phagophore to the damaged mitochondria and leading to its degradation [37]. In addition, PINK1 can directly recruit nuclear dot protein 52 (NDP52) to mitochondria, to directly activate mitophagy that is independent of Parkin [38].

Parkin and PINK1 are also involved in a vesicular pathway regulating MQC, known as MDVs. This pathway is distinct from canonical mitophagy and is triggered by the generation of oxidative stress from within mitochondria. Vesicles bud off of damaged mitochondria and are degraded in the lysosome [39]. MDVs are selectively enriched for oxidized proteins and damaged mitochondrial contents and may regulate mitochondrial quality faster than mitophagy [40]. In addition, similar to autophagosomes, a structurally unique kind of mitochondria called mitochondrial spheroids were also found to serve as an alternative pathway for regulation of mitochondrial homeostasis [41]. Mutations in PINK1 or Parkin cause the accumulation of dysfunctional mitochondria, which in turn leads to an increase in ROS and, ultimately, to neurodegeneration. These mutations can lead to the loss of dopaminergic neurons in the substantia nigra, which is directly related to the pathogenesis of Parkinson's disease (PD) [42].

Mitochondria lie at the crossroads of neuronal survival and cell death. Mitochondria have evolved strategies to kill cells when they are not rescued by the above several MQC pathways and are not able to continue their vital functions [43]. Mitochondrial permeability transition pore (mPTP)-induced apoptosis is one of the cell death pathways. The composition of mPTP includes voltage-dependent anion channel (VDAC), adenine nucleotide translocase (ANT), and cyclophilin-D (CypD) [44]. Following mPTP opening, cytochrome C (CytC) can be released [45]. In the cytoplasm, CytC binds to apoptotic protease activating factor 1 (Apaf-1)

to form an apoptosome and mediates apoptosis [46] (Fig. 1). Excessive apoptotic cell death has been implicated in the pathogenesis of many human NDDs [47].

In neurons, MQC involves many proteins and has multiple roles. When investigating the specific mechanisms of MQC, a key molecule, PGC-1α, came to our attention. Previous studies into PGC-1α have focused on its regulation of mitochondrial energy metabolism and biogenesis. However, recent studies have shown that, in NDDs, PGC-1α is also important in MQC through the regulation of the aforementioned proteins.

PGC-1α and Its Regulation of Mitochondrial Biogenesis and Mitochondrial Energy Metabolism

PGC-1α is a transcriptional coactivator that is abundant in the brain [48]. In addition to its localization in the nucleus, the 35 kDa PGC-1α (NT-PGC-1α) is also localized to mitochondria [49, 50] (Fig. 2). PGC-1α dynamically responds to the regulation of multiple upstream signaling pathway proteins at both the transcriptional and post-translational levels [51].

Mitochondrial dysfunction in the nervous system may lead to serious consequences, including severe energy insufficiency, impaired calcium buffering and increased ROS generation [52]. When the intracellular AMP/ATP ratio increases, the Ser/Thr kinase AMP-activated protein kinase (AMPK) is activated [53], and AMPK then activates PGC-1α by phosphorylation [54]. The acute actions of AMPK on lipid oxidation can also alter the balance between cellular NAD^+ and NADH [55], and when the ratio of NAD^+/NADH increases [56], sirtuin-2-related enzyme 1 (Sirt1) activates PGC-1α by deacetylation [57, 58]. When the ratio of NAD^+/NADH is decreased, the coactivator steroid receptor coactivator-3 (SRC-3) induces the expression of the lysine acetyltransferase GCN5, and GCN5 then acetylates PGC-1α to inhibit its activity [59]. Mitochondrial Ca^{2+} overload leads to the transcription of PGC-1α [60], and Ca^{2+} signaling can induce cAMP-response element binding protein (CREB) phosphorylation via calmodulin-dependent protein kinase IV (CaMKIV), which then mediates PGC-1a transcription [61, 62]. Ca^{2+} can also activate AMPK, which in turn activates PGC-α [63]. In Huntington's disease (HD), transducer of regulated CREB (TORC) strongly regulates the activity of the PGC-1α promoter and promotes its high expression [64]. In PD, the protease Omi prevents the degradation of PGC-1a by cutting glycogen synthase kinase 3β (GSK3β) [65]. PGC-1α can also be induced by

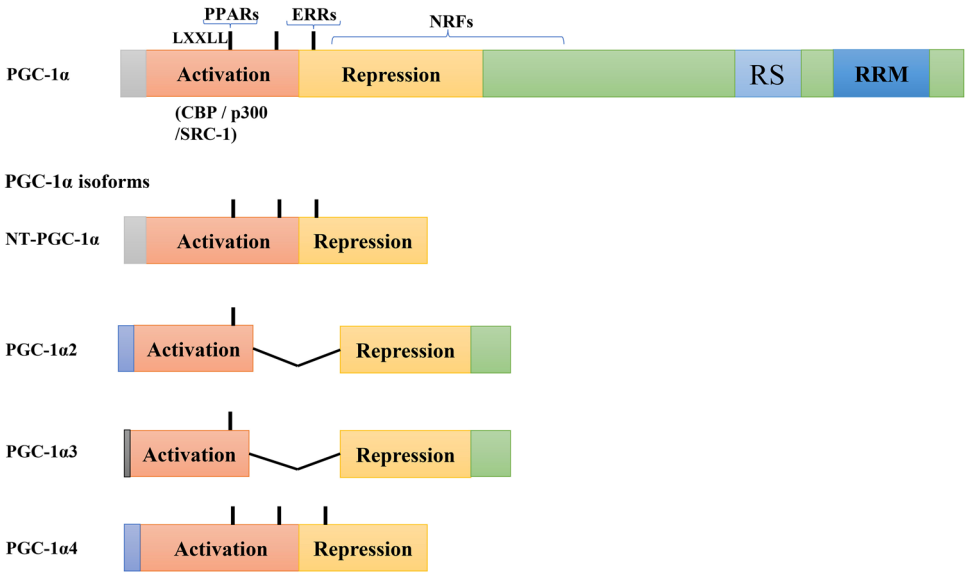

Fig. 2 The structure of PGC-1α and its isoforms. The N-terminus of PGC-1α has a protein activation domain and three leucine-rich LXXLL motifs, as well as a repression domain. The C-terminus has a serine–arginine-rich RS region and an RNA recognition motif (RRM). The activation domain is responsible for interactions with several histone acetyltransferase (HAT) complexes, including CREB-binding protein/p300 (CBP/p300) and steroid receptor coactivator-1 (SRC-1), which promote gene transcription. The LXXLL motif mediates the interaction of PGC-1α with transcription factors and other coactivator complexes, including PPARs and ERRs. The repression domain is involved in the inhibition of PGC-1α activity, while the RS and RRM domains are characteristic of proteins involved in RNA splicing. PGC-1α produces many isoforms by using multiple promoters and alternative splicing, which include NT-PGC-1α and PGC-1α2/3/4, among others

ROS [66]. Impaired mitochondria accelerate ROS production, and increased ROS activate AMPK, which in turn activates PGC-1α [67]. Activated PGC-1α does not bind to DNA itself, but enhances the activity of true DNA-binding transcription factors [26], which include nuclear respiratory factors (NRF-1 and NRF-2) [68], PPARs (PPARα, PPARδ, and PPARγ) [69], and estrogen-related receptors (ERRα, ERRβ, and ERRγ) [70]. This increased activity promotes the transcription of mitochondrial regulatory proteins, leading to neuroprotection.

As mitochondria are not synthesized from the beginning, they could proliferate from the ones already existing to keep biogenesis [71]. Mitochondrial biogenesis assumes a critical part to keep mitochondrial homeostasis and meet the physiological demands of eukaryotic cells [72]. Damaged mitochondrial components can also be replaced by mitochondrial biogenesis [73]. Moreover, strong research evidence recommends a probable reduction in ROS production by the biogenesis of a significant density of functional mitochondria [74]. The drug bezafibrate activates the expression of downstream targets involved in mitochondrial biosynthesis (including TFAM, CytC, and ATP synthase) via the PGC-1α-PPARs pathway, thus improving oxidative stress and increasing mitochondrial biogenesis. This in turn reduces astrocyte proliferation [75].

In terms of energy metabolism, the PGC-1α-NRF-1 signaling pathway activates the OXPHOS component and promotes the expression of mitochondrial complexes I, II, III, IV, and CytC. This signaling pathway is critical for the pathogenesis of HD [76]. In addition, the PGC-1α-NRFs-TFAM pathway regulates oxidation–reduction reactions and confers anti-oxidant and pro-survival effects, which may contribute to neuroprotection in NDDs [77, 78]. ERRs regulate almost all mitochondrial functions, including fatty acid β-oxidation (FAO), the tricarboxylic acid cycle (TAC), mtDNA replication, OXPHOS, and ETCs [70]. The PGC-1α-ERRγ signaling pathway exerts neuroprotective effects against cell death in a PD model [79].

PGC-1α Regulates MQC in NDDs

NDDs can lead to the deterioration of the structure and function of nerve tissue, causing irreversible damage. NDDs usually manifest as specific neuronal group damage, cognitive dysfunction, or motor coordination disorders, and affect the behavior and personality of individuals with the disorders [1]. Numerous studies have shown that the pathogenesis of HD, AD, and PD involves PGC-1α-mediated MQC. In these major NDDs, the expression level and activity of PGC-1α are downregulated, and MQC is impaired [54, 80, 81]. Increasing PGC-1α levels to regulate MQC, thereby reducing nerve damage, may therefore be a promising treatment for NDDs [82] (Fig. 3).

HD

HD is caused by the amplification of a CAG repeat in the gene that encodes huntingtin, which leads to an extended N-terminal polyglutamine sequence in the huntingtin protein (HTT) [83]. In striatal cells of HD patients, the activity of mitochondrial oxidative phosphorylation complex II, III is decreased [84, 85], and the activity of the aconitase in the basal ganglia of patients is also decreased [86]. This causes severe damage to mitochondrial respiration and ATP production, and large quantities of ROS are then produced [87], which in turn cause damage to mtDNA and the misfolding of proteins [88]. In the neurons of HD mice, mHTT triggers mitochondrial fission [89] and reduces Mfn1, which is involved in mitochondrial fusion [90, 91]. In the absence of fusion, excessive mitochondrial fission results in a decrease in mtDNA-encoded respiratory chain subunits and the inhibition of ATP synthesis, which then results in neuronal energy deficits [92]. Excessive mitochondrial fission triggered by mHTT also causes abnormalities in the ultrastructure of mitochondria, impaired calcium buffering, and a loss of mtDNA [93]. In addition, mHTT prevents autophagosome fusion with lysosomes [94, 95], thus impairing mitophagy.

At the molecular level, PGC-1α enhances chaperone and protease activity by modulating mtUPR, thereby refolding or degrading misfolded proteins. This prevents mitochondrial dysfunction caused by the massive accumulation of damaged proteins, and reduces neuronal damage [10]. PGC-1α can co-activate the transcription factor NRF-2, which binds to the binding site of the Lon promoter region and upregulates Lon protease [96] to remove these damaged proteins. In addition, PGC-1α interacts with ERRα, which binds to the Sirt3 promoter as its transcription factor to regulate Sirt3 expression [97]. Sirt3 is one of the important coordinators of mtUPR [88].

At the organellar level, PGC-1α can slow the excessive fission of mitochondria while increasing the levels of mitochondrial fusion, and thus plays a role in regulating the balance between neuronal mitochondrial fission and fusion. This can prevent or slow down the damage and denaturation of neuronal axons caused by mitochondrial-fragmentation-induced insufficient ATP supply. Studies have also shown that PGC-1α can regulate the expression of Drp1 [98]. Activation of PPARγ reduces the expression of p-Drp1 (serine 616 phosphorylation), thereby reducing excessive mitochondrial fission and reducing neuronal damage in the hippocampal CA1 subregion [99]. PGC-1α binds to the Mfn-2 promoter in a region centered on the

ERRα binding element, regulates Mfn-2 expression, and promotes mitochondrial fusion [100]. In addition to the role of PGC-1α in the co-activation of ROS defense gene expression, PGC-1α also binds to the transcription factor EB (TFEB) promoter, promoting ubiquitin–proteasome system (UPS) function, which helps to reduce mHTT aggregates [101].

AD

AD is an age-related NDD characterized by an overproduction of Aβ peptide and an aggregation of phosphorylated tau proteins in different regions of the brain, but particularly in the hippocampus, which is closely related to learning and memory [102–104]. Aβ disrupts complex IV function, and tau primarily impairs the activity of ETC complex I [105, 106], and this increases ROS levels and inhibits ATP production. At the molecular level, PGC-1α can control the level of damaged or misfolded proteins by upregulating Lon protease expression and coordinating mtUPR to reduce neuronal damage and delay the progression of AD [96, 107].

In terms of mitochondrial fusion and fission, Aβ leads to increased fission and decreased fusion, which results in mitochondrial fragmentation and reduced mitochondrial density, leading to a large number of smaller and structurally damaged mitochondria. These mitochondria have a loss of directional motion and a change in synaptic localization [108–112]. By establishing cell models of PGC-1α overexpression and reduced expression, Peng K et al. found that PGC-1α can regulate MFN2 and Drp1 protein expression and phosphorylation to influence mitochondrial fission/fusion, thereby maintaining the delicate equilibrium between mitochondrial fission and fusion [113]. In addition, it has been experimentally confirmed that the expression of PGC-1α in AD neurons promotes the non-amyloidosis processing of amyloid precursor protein (APP), which attenuates the production of Aβ [114]. PPARγ is upregulated in a PGC-1α-dependent manner [115], and upregulated PPARγ reduces the activity of the β-site APP-cleaving enzyme 1 (BACE1) promoter, which is a key enzyme in Aβ production [116]. This in turn reduces Aβ production, thus reducing its damage of MQC. Tau disrupts the binding of Drp1 to mitochondria, leading to mitochondrial elongation, and this impedes mitochondrial transport, enhances oxidative stress, and causes mitochondrial membrane potential depletion and neurodegeneration in cortical neurons [117, 118]. Nuclear factor E2-related factor 2 (Nrf2) reduces phosphorylated tau protein levels by inducing the expression of the autophagy adaptor protein NDP52 [119], while the expression of Nrf2 exhibits PPARγ dependence [120]. It has been reported that the autophagy flux in AD and AD models is significantly impaired, and damaged mitochondria therefore accumulate in this disease [121, 122]. NDP52 is also an important autophagy receptor for mitophagy, and its high expression can rescue mitophagy [123]. Mitophagy activated by the PGC-1α-PPARγ-Nrf2-NDP52 pathway may thus help to reduce the pathogenesis of AD. In addition, PGC-1α activates ERRα to promote the transcription of *Sirt3*, thereby inhibiting phosphorylation of the mammalian target of rapamycine (mTOR), which leads to increased expression of LC3 and Beclin-1. This inhibited phosphorylation also promotes the translocation of p62 to damaged mitochondria, where it exerts neuroprotective effects by promoting mitophagy [124, 125].

PD

PD is an NDD with pathology featuring the loss of dopaminergic neurons and the presence of α-synuclein (α-syn)-containing Lewy bodies in the substantia nigra pars compacta (SNpc), with a subsequent decrease in striatal dopamine levels [126]. Previous studies have revealed that mitochondrial dysfunction and oxidative stress are associated with the pathogenesis of PD [127, 128]. According to latest research, MQC dysfunction is also a mechanism of PD pathogenesis [129].

Lon protease in PD patients is particularly prone to inactivation in the mitochondria of the SNpc [130]. This inactivation leads to the accumulation of oxidized proteins such as glucuronidase and cis-aconitase, which are sensitive to oxidative inactivation [131]. The accumulation of these oxidized proteins results in mitochondrial dysfunction. At the molecular level, PGC-1α can co-activate the transcription factor NRF-2, which binds to the binding site of the Lon promoter nt-623/+1 region and upregulates Lon protease [96]. This upregulation maintains a sufficient level of active Lon protease to remove oxidized proteins and exert neuroprotective effects [132].

α-Syn negatively regulates autophagosome synthesis, leading to defects in mitophagy, which results in the accumulation of dysfunctional mitochondria, increased ROS, and ultimately neurodegeneration [133]. PGC-1α reduces α-syn oligomerization and improves α-syn-mediated toxicity, reducing the loss of dopaminergic neurons that is induced by mutant α-syn [134]. In addition, studies have shown that PGC-1α and PINK1 interact at both the transcriptional and translational levels. NT-PGC-1α binds to and colocalizes with PINK1 in brain mitochondria [49, 50, 135]. Furthermore, nuclear 91 kDa PGC-1α-mediated transcriptional control may potentially activate the PINK1 promoter, and overexpression of PGC-1α results in the increased expression of PINK1 in cells [136]. PGC-1α can also indirectly activate the PINK1-Parkin pathway via the ERRα-Sirt3 pathway, thus mediating the translocation of Parkin to

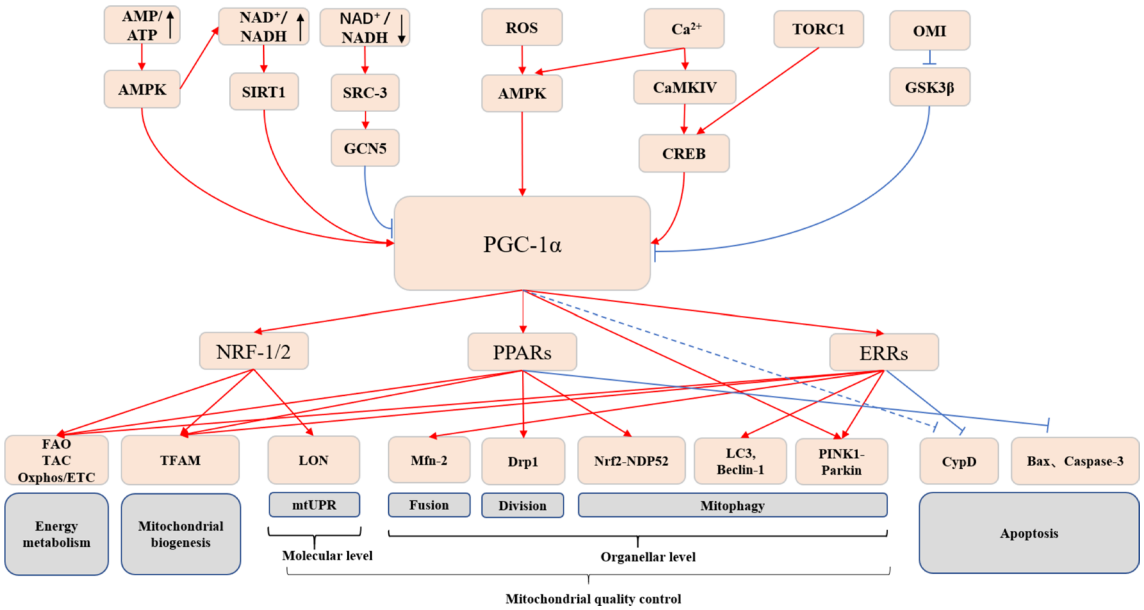

Fig. 3 PGC-1α: a transcriptional coactivator in neural cells. A variety of upstream signaling pathways can upregulate or downregulate the expression and/or the activity of PGC-1α. Through interactions with NRFs, PPARs, and ERRs, PGC-1α affects the expression of many genes involved in mitochondrial energy metabolism, biogenesis, and quality control. PGC-1α plays an important neuroprotective role in neurons through the regulation of multiple quality control pathways. In this figure, red arrows indicate activation, blue lines indicate inhibition, and dotted lines indicate that the mechanism is not yet clear (Color figure online)

damaged mitochondria, and thereby delaying mitochondrial damage and the degeneration and necrosis of dopaminergic neurons that is induced by mutant PINK1 [137]. In addition, the reciprocal positive feedforward PGC1α-TFEB signaling pathway in the Q311X Parkin mutant mouse can promote autophagy to remove damaged mitochondria and exert neuroprotective functions [138].

In NDDs, PGC-1α can inhibit apoptosis by protecting mitochondrial function and reducing the expression of apoptotic proteins. The excessive mitochondrial fission and inhibition of fusion leads to ultrastructural changes in mitochondrial cristae, promotes CytC release, and increases sensitivity to apoptosis [139]. Experiments by Taiji Tsunemi et al. demonstrated that upregulation of PGC-1α expression prevents HTT-104Q-dependent apoptotic cell death [101]. In AD, Aβ binds to CypD and promotes its translocation to IMM. This promotes the opening of mPTP [140]. It has been observed that CypD is downregulated in mice that overexpress PGC-1α in skeletal muscle, and this leads to a decrease in mPTP sensitivity [141]. PGC-1α also deacetylates CypD via the ERRα-Sirt3 pathway, which inactivates CypD [142]. In addition, PGC-1α reduces the expression of apoptotic proteins such as Bcl-2-associated X protein (Bax) and Caspase-3 by co-activating PPARγ [143].

Future Directions

In terms of recognized therapeutic targets, PGC-1α and PPARγ agonists are being developed, and some are already in use to protect the brain against diverse stimuli and damages. MitoQ, a mitochondria-targeted antioxidant, can protect DA neurons in 6-hydroxydopamine-induced PD model by activating PGC-1α to enhance Mfn2-dependent mitochondrial fusion [82]. Bezafibrate, a pan-PPAR agonist, increases the expression of PGC-1α and mitochondrial biogenesis, and improves phenotype and survival in R6/2 transgenic mouse model of HD [144]. Dexmedetomidine (DEX), a central adrenoceptor α-2A agonist, reduces oxidative stress and provides neuroprotection in a model of traumatic brain injury via the PGC-1α signaling pathway [145]. The pharmacological induction of PGC-1α expression may be considered in the future as a neuroprotective approach, but this possibility is currently limited by the reduced blood–brain barrier penetration of potential pharmaceutical agents [146]. Further research is therefore needed to improve the efficiency and permeability of drugs that induce the expression of PGC-1α, so that they are more conducive to the treatment of NDDs. In addition, studies have shown that continued overexpression of PGC-1α can lead to major alterations in the metabolic activity of neuronal cells, dramatically impairing dopaminergic function in vivo [147]. It thus appears critical to design therapeutic strategies

that maintain a tight, physiological regulation of PGC-1α expression.

To date, more than ten novel PGC-1α isoforms have been reported owing to its multiple promoters and alternative splicing. NT-PGC-1α can localize to mitochondria and is associated with the maintenance of mitochondrial integrity. RitaTorok et al.'s research shows that after the high-dose acute treatment regimen of the complex I inhibitor mPTP, the expression levels of NT-PGC-1α isoforms increased significantly in the striatum, cortex and cerebellum [146]. PGC-1α2 and α3 have distinct first exons but have the same remaining exon/intron structure. PGC-1α4 shares the same alternative exon1 with PGC-1α2 [148]. PGC-1α2 mediates a decrease in the levels of cholesterol synthesis genes [149]. Furthermore, the PGC-1α2 is involved in skeletal muscle regeneration, and PGC-1α3 is involved in cell cycle regulation [148, 149]. PGC-1α4 is highly expressed in exercised muscle but does not regulate most known PGC-1α targets such as the mitochondrial OXPHOS genes. PGC-1α4 regulates distinct target gene networks involved in hypertrophy in skeletal muscle [148]. The specific roles and mechanisms of PGC-1α2/3/4 in the nervous system remain to be studied.

As well as its role in NDDs, PGC-1α also promotes insulin secretion coupled to fatty acids by regulating β cell lipid metabolism in diabetes [150]. In myocardial ischemia–reperfusion studies, PGC-1α also protects myocardial mitochondria by regulating mitochondrial energy metabolism and improving oxidative stress [151]. These studies suggest that PGC-1α may play a role in a variety of diseases.

Conclusions

There is increasing evidence that activation of PGC-1α can reduce neuronal degeneration and mediate neuroprotection by regulating energy metabolism, mitochondrial biogenesis, and MQC. We believe that MQC is most important for this neuroprotective effect. The present review describes the multi-level regulation by PGC-1α of neuronal MQC in NDDs by analyzing various signaling pathways of PGC-1α. However, the PGC-1α signaling pathway in neurons is very complex, and many upstream signal pathways and downstream effectors also provide opportunities for future exploration. What is currently known may be just the tip of the iceberg. In addition, the regulation of MQC by PGC-1α in neurons is still incompletely understood, and further research is needed before PGC-1α can be considered as a treatment for NDDs.

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