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Review article

Diverse roles of mitochondria in ischemic stroke

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ABSTRACT

Stroke is the leading cause of adult disability and mortality in most developing and developed countries. The current best practices for patients with acute ischemic stroke include intravenous tissue plasminogen activator and endovascular thrombectomy for large-vessel occlusion to improve clinical outcomes. However, only a limited portion of patients receive thrombolytic therapy or endovascular treatment because the therapeutic time window after ischemic stroke is narrow. To address the current shortage of stroke management approaches, it is critical to identify new potential therapeutic targets. The mitochondrion is an often overlooked target for the clinical treatment of stroke. Early studies of mitochondria focused on their bioenergetic role; however, these organelles are now known to be important in a wide range of cellular functions and signaling events. This review aims to summarize the current knowledge on the mitochondrial molecular mechanisms underlying cerebral ischemia and involved in reactive oxygen species generation and scavenging, electron transport chain dysfunction, apoptosis, mitochondrial dynamics and biogenesis, and inflammation. A better understanding of the roles of mitochondria in ischemia-related neuronal death and protection may provide a rationale for the development of innovative therapeutic regimens for ischemic stroke and other stroke syndromes.

1. Introduction

Stroke is the leading cause of physical and intellectual disability in adults and remains the major cause of mortality in the developed countries. Data from the World Health Organization (WHO) suggest that around 15 million people suffer stroke each year globally. Of these, 5 million die and another 5 million remain disabled permanently, putting a tremendous burden on the family and society. The stroke burden is projected to rise from around 38 million disability-adjusted life years (DALYs) globally in 1990 to 61 million DALYs in 2020. (The Atlas of Heart Disease and Stroke from http://www.who.int/cardiovascular_diseases/resources/atlas/en/). A large majority (80–90%) of stroke cases are caused by thrombotic or embolic events [1,2]. Currently, the first-line treatment guideline for acute ischemic stroke is intravenous recombinant tissue-type plasminogen activator (tPA) [3]. Intravenous tPA needs to be administered within 3 h of having a stroke (up to 4.5 h in certain eligible patients), and the patient must meet multiple selection criteria [4]. However, at most around 8% of stroke patients eligible for tPA receive it because of the limited treatment time window [5]. Endovascular thrombectomy becomes the standard treatment for acute stroke patients with large-vessel occlusion [6]. The review guidelines "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment" are based on the results of 5 recent clinical trials, including MR CLEAN [7], ESCAPE [8], EXTEND-IA [9], SWIFT-PRIME [10], and REVASCAT [11]. According to these guidelines, endovascular procedures must be performed within 6 h after stroke onset, a time window only slightly longer than that for tPA treatment. Currently, most of the acute ischemic stroke patients receive no active treatment. Thus, the main goal of stroke research is to develop effective treatments to reduce brain impairment from ischemic insult through a better understanding of the underlying pathogenic molecular mechanisms.

Mitochondria are widely distributed intracellular organelles enclosed by a double membrane. The outer phospholipid bilayer membrane contains protein channel structures rendering the membrane permeable to molecules of up to 10 kDa, such as ions, water, nutrient molecules, and adenosine di- and triphosphate (ADP and ATP). The inner membrane is the reactive center of mitochondrial energy metabolism, containing complexes of electron transport proteins, the ATP

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synthetase complex, and ATP/ADP transport proteins; it is permeable to oxygen, carbon dioxide, and water. The principal role of mitochondria is to generate cellular energy in the form of ATP by the mitochondrial electron transport chain (ETC) through oxidative phosphorylation. Mitochondrial oxidative phosphorylation involves multi-enzyme complexes (complexes I–V) located in the mitochondrial inner membrane [12]. These include the proton-pumping enzyme complex I (nicotinamide adenine dinucleotide [NADH]–ubiquinone oxidoreductase), cytochrome bc_1 complex III, and cytochrome *c* oxidase complex IV, which together produce a proton motive force that drives ATP generation by complex IV (F_1F_0-ATP synthase). Electron transport among complexes is mediated by membrane-embedded ubiquinone (Q) and soluble cytochrome *c*. Complex I is the access point for electrons from NADH to reduce Q to ubiquinol (QH_2). Complex II (succinate–quinone oxidoreductase) offers an additional entrance point for electrons of QH_2 into the respiration chain. Cytochrome *c* is reduced by complex III with electrons from complex II in the intermembrane space (IMS). In the subsequent reaction, cytochrome *c* is oxidized by complex IV to reduce oxygen, the ultimate electron acceptor [12,13]. Biochemical evidence suggests that the greater portion of cerebral ATP is consumed for neuronal electrogenic activity [14]. An adequate amount of energy supply by mitochondria is thus crucial for neuronal excitability and survival. In addition to energy production, mitochondria are the major source of reactive oxygen species (ROS) and serve as apoptotic regulators [15,16]. Both these functions have been critically implicated in the pathogenesis of neurodegenerative diseases and cerebral ischemia [16,17].

Accumulating evidence suggests a tight relationship between ROS overproduction and neuronal death in various neurological disorders, including amyotrophic lateral sclerosis (ALS), epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, and traumatic brain injury [18,19]. Excessive ROS levels cause both functional and structural impairment of brain tissue and play a pivotal role in the pathogenesis of cerebral ischemia [20–22]. The critical role of dysfunctional mitochondria, as well as excessive oxidative stress, in ischemic cascades is well established. Therefore, amelioration of the harmful effects of oxidative stress through a better understanding of apoptotic and necrotic neuronal injury holds promise for the management of ROS-related diseases such as ischemic stroke. Recent studies have revealed that an ROS-detoxifying system and mitochondrial biogenesis are the 2 main endogenous protective mechanisms involved in chronic neurodegenerative diseases and acute cerebral ischemia [23–25].

Mitochondria are dynamic organelles that retain their morphology through two opposite processes: fission and fusion. While the fission process includes the constriction and cleavage of mitochondria, the fusion process involves the elongation of mitochondria by the joining and tethering of the mitochondria in close proximity [26–28]. Dynamin-related protein 1 (Drp1) is a mitochondrial-binding GTPase that mediates mitochondrial fission [29]. At present, mitochondrial dynamics has emerged as a crucial process in the regulation of cell survival and death; particularly, mitochondrial fission precedes neuronal death after cerebral ischemia [30–32]. Global cerebral ischemia causes a transient increase in the phosphorylation of Drp1 at serine 616 [p-Drp1(Ser616)] without notably affecting total Drp1 protein expression or its phosphorylation at serine 637 in hippocampal CA1 neurons [33]. Furthermore, Drp1 inhibitors reduced the infarct volume in a focal cerebral ischemia model [31,32,34], suggesting that mitochondrial dynamics has a vital function in ischemic neuronal injury and recovery.

Autophagy is a biological, ordered, and destructive mechanism of the cell that serves to eliminate unwarranted or dysfunctional components [35]. It is a system for the degradation of intracellular components. Except for the rapid removal of damaged organelles, the unique role of autophagy is to provide nutrients that maintain metabolism in response to the cellular nourishing conditions. Accurate management of all the constituents in the autophagic system is crucial for the maintenance of intracellular homeostasis and survival during differentiation, normal growth control, and starvation [36–40]. Autophagy is the main degradative pathway for mitochondrial turnover, and mitochondrial autophagy is often called “mitophagy” [41]. The protective role of autophagy during ischemia/reperfusion may be attributable to mitophagy-related mitochondrial clearance and inhibition of downstream apoptosis [42]. In contrast, uncontrolled autophagy may lead to unrestrained digestion of affected neurons and neuronal death in cerebral ischemia. Therefore, stringent mitochondrial quality control mechanisms are imperative to maintain a healthy mitochondrial network with efficient coordination. Mitophagy is the crucial process guarding mitochondrial quality and function as well as determining cell fates.

Inflammation is another pivotal mechanism in the pathogenesis of cerebral ischemia. The post-ischemia inflammatory response is initiated by glial cell activation, peripheral leukocyte infiltration, and damage-associated molecules such as high-mobility group protein 1, nucleic acid fragments, nucleotides, and purines [43,44]. In addition, acute systemic inflammatory stimuli worsen ischemic stroke outcomes, with the pro-inflammatory cytokine, interleukin-1β (IL-1β), acting a critical mediator [45]. Recent studies have recognized emerging roles of mitochondria in the regulation of the inflammatory response [46–48]. Mitochondria are the main modulators of NLR family pyrin-domain-containing protein 3 (NLRP3) inflammasome activation [49]: the outer mitochondrial membrane serves as a platform for inflammasome assembly and activates innate immune defense and pyroptosis through several pro-inflammatory cytokines and caspase-1 [50,51]. Multiple recent studies have reported emerging roles of the NLRP3 inflammasome in heart and renal ischemia [52–55], which may be similar to its function in cerebral ischemia.

This review will focus on the evolving multifaceted role of mitochondria in cerebral ischemic stroke. Understanding the underlying mechanisms of potentially protective mitochondrial functions may provide a rationale for the development of new therapeutic regimens for ischemic stroke and other stroke syndromes.

2. Cerebral ischemic cascade involves mitochondrial function and ROS

An ischemic event occurs when the blood flow to the brain tissue supplied by occluded arteries is decreased. The lack of oxygen and nutrients leads to disturbed cellular homeostasis and, eventually, cell death. The pathophysiology of cerebral ischemia has been well characterized in animal models of stroke [56–58]. In an ischemic stroke patient, a significant decline in the focal cerebral blood flow leads to deprivation of glucose and oxygen and causes brain damage. Treatments such as tissue plasminogen activator administration or endovascular thrombectomy, the current limited stroke treatment alternatives, can recanalize the occlusion and induce reperfusion of the vessels. During reperfusion, oxygen is restored, which is critical for maintaining neuronal viability. However, both, the pro-oxidant enzymic system and mitochondria can also employ oxygen as a substrate to generate substantial amounts of oxygen free radicals during reperfusion [59]. The schematic diagram in Fig. 1 illustrates the cellular and molecular processes and events leading to ischemic neuronal death. In this section, we discuss the detrimental effects of excessive oxidative stress generated by mitochondria in the ischemic brain.

Oxidative stress is defined as an imbalance between ROS production and the capability to readily neutralize the reactive intermediate products in a biological system. The consequences of oxidative stress depend on the magnitude of changes in the levels of ROS and their derivatives. A small change in ROS abundance may be negated by the endogenous antioxidant system. However, severe oxidative stress can result in cell death through an apoptotic or necrotic pathway [60]. ROS are generated in living cells under various stimuli, including hypoxia, cerebral ischemia, cytokine stimulation, and serum deprivation, by a number of sources, with mitochondria, 5-lipoxygenase, and NADPH

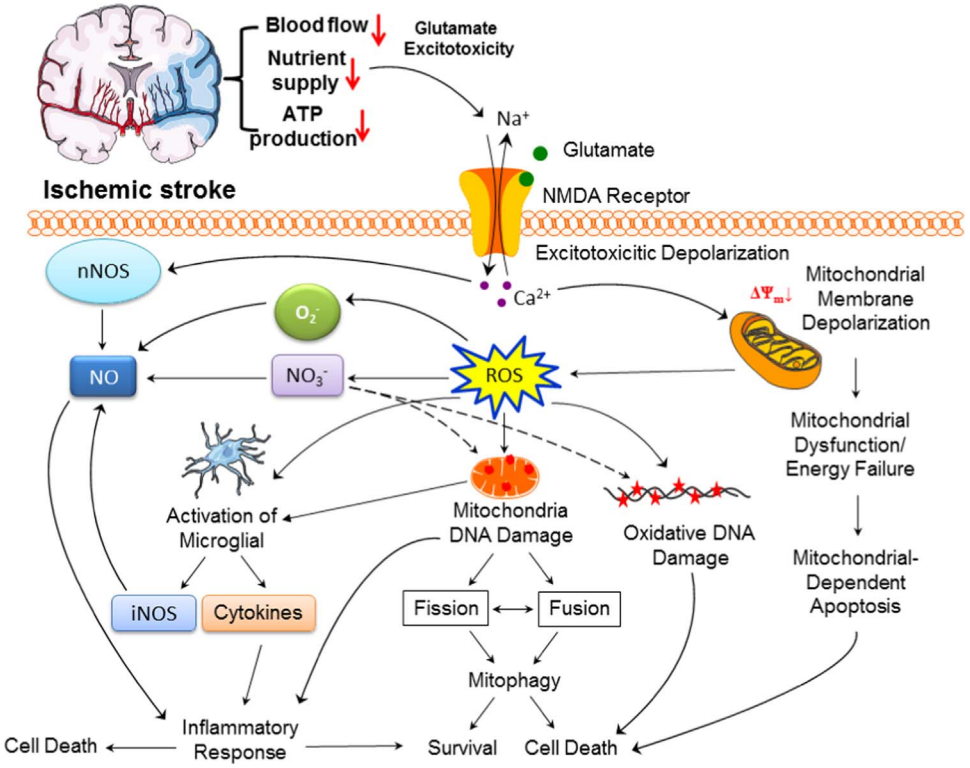

Fig. 1. Pathological signaling pathways involved in mitochondrial function and reactive oxygen species (ROS) generation in the cerebral ischemic cascade. The downstream signaling pathways of ischemic-stroke-induced glutamate excitotoxicity are schematically shown. Excessive Ca^{2+} influx causes mitochondrial dysfunction and ROS production, leading to various pathological processes, such as mitochondrion-dependent apoptosis, mitochondrial fission and fusion, mitophagy, and DNA damage response and inflammatory responses. Some of these cellular processes eventually lead to cell death. NMDA, N-methyl-D-aspartate; iNOS, inducible NOS; nNOS, neuronal NOS; NO, nitric oxide; NOS, NO synthase.

oxidase representing the main ones [61,62]. Mitochondria are the major source of intracellular ROS [16,61,63,64]. With continued oxidative stress, free electrons in the mitochondrial ETC may leak out and react with molecular oxygen, generating superoxide anion (O_2^-) as a metabolic byproduct of respiration. The highly active O_2^- reacts into the nitrogen oxide (NO)-forming peroxynitrite anion (NO_3^-), which in turn leads to the formation of the cytotoxic hydroxyl radical and alterations in the structures of DNA, proteins, and lipids [65]. Excessive NO formation is mediated by various isoforms of nitric oxide synthase (NOS) activated post-ischemic stroke, including neuronal, endothelial, and inducible NOSs. Modification of macromolecules by ROS and reactive nitrogen species (RNS) plays a pivotal role in numerous physiological and pathological conditions, particularly cancer, neurodegenerative diseases, and ischemia-reperfusion injury [21,66–68]. In addition, recent studies have suggested that nitrosative stress due to the generation of excessive NO mediates excitotoxicity in part by triggering protein misfolding, aggregation, and mitochondrial fragmentation [69]. S-Nitrosylation, the covalent reaction of NO with specific protein thiol groups, represents a convergent signaling pathway contributing to NO-induced protein misfolding and aggregation, which may compromise the dynamics of the mitochondrial fission-fusion process and thus lead to neurotoxicity [69].

Thus, it is essential to keep low ROS levels for normal cell function, while expanded elevation of mitochondrial activity has an intrinsic risk of increased ROS levels. Following cerebral ischemia, the balance between ROS production and clearance is compromised, resulting in oxidative-stress-induced signaling and cell injury. The pathogenic role of free radicals in ischemic brain injury has been reviewed in detail elsewhere [59,70,71].

3. Proteins involved in mitochondrion-dependent apoptosis in cerebral ischemia

The emerging complexities of the molecular mechanisms triggering cell death in neurological disorders, such as neurodegeneration and seizure, are also involved in cerebral ischemia [24,72]. Ischemia-induced cell death reflects a transition and from cellular pro-survival responses to activated pro-death factors over hours or even days. Programmed, controlled cell death (apoptosis) and passive, uncontrolled cell death (necrosis) are commonly observed in the ischemic brain. However, each apoptotic or necrotic process occurs in a distinct injured region, albeit it can be mixed in some areas. After cerebral ischemia, mitochondria produce increased amounts of ROS. In addition to directly damaging lipids, proteins, and nucleic acids in the cell, ROS can trigger a variety of molecular signaling pathways. Of these, apoptosis can be initiated by involving the disruption of mitochondria, and subsequently inducing cell death through the release of pro-apoptotic proteins such as cytochrome *c* or apoptosis-inducing factor [16].

A critical role of neuronal apoptosis in ischemia-induced brain injury has been shown in both human and animal studies [73–76]. Various conditions and factors affect the process leading to cell death, including ischemia duration and severity, metabolic deregulation, bioenergetic breakdown, genetic factors, and ageing [77,78]. A crucial determination of the cell death process relies on the intracellular ATP concentration, since ATP production tightly depends on the integrity of mitochondrial structure and function. While ATP is required for apoptosis, an ATP deficiency is associated with necrosis in the injured cell [79].

In ischemic stroke, a necrotic core is surrounded by a peri-infarct zone known as the “ischemic penumbra”, consisting of functionally impaired yet still viable tissue. The injured neurons of the penumbral area likely can be salvaged with post-stroke treatment [80]. Recent studies have revealed that neurons in the ischemic penumbra may undergo apoptosis hours or days after ischemia [81–83], opening a window of opportunity for their rescue. Intervention in the penumbral area to halt or suppress the apoptotic process is an attainable therapeutic goal aimed to limit the infarct volume after clinical stroke. A thorough understanding of the apoptotic mechanisms in cerebral ischemia is required to develop such novel therapeutic interventions.

In addition to being known as cellular powerhouses, mitochondria appear to play a key role in the cell death machinery because of their associations with a long list of apoptosis-related proteins [84,85].

Accumulating evidence suggests that a group of proteins of the B-cell lymphoma (BCL-2) family are profoundly involved in the regulation of neuronal death in cerebral ischemic stroke [86–90]. The BCL-2 protein family is a major regulator of outer mitochondrial membrane permeability and plays critical roles in the intrinsic apoptotic pathway [91]. The BCL-2 family has been classified into 2 groups based on structural homology and function: anti-apoptotic proteins, including Bcl-2, Bcl-xL, and Bcl-w, and pro-apoptotic proteins, such as Bax, Bak, Bim, Bid, Bad, Noxa, and p53-upregulated modulator of apoptosis [16,91]. Many studies have indicated that the pro-apoptotic BH3-only BCL-2 subfamily is upregulated after cerebral ischemia, suggesting that ischemic stroke elicits multiple apoptotic pathways involving mitochondria [22,92–94]. The activities of anti- and pro-apoptotic proteins are correlated with mitochondrial function and the ROS concentration.

In addition to the BCL-2 pathway, several other major apoptotic pathways originate in mitochondria and involve the release of pro-apoptotic factors (such as apoptosis-inducing factor [AIF], cytochrome c, endonuclease G, high-temperature requirement protein A (HtrA2/OMI), and second mitochondrion-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI [SMAC/DIABLO]), changes in the mitochondrial ETC, altered cellular redox homeostasis, and loss of the mitochondrial transmembrane potential [84,95]. Another critical process along the apoptotic cascade is linked to mitochondrial permeability transition pores (MPTPs) in the mitochondrial inner membrane [96]. A transient opening of MPTPs is induced by various conditions of cellular stress, which results in the initiation of the apoptotic cascade through a collapse of the mitochondrial transmembrane potential. The latter event triggers the release of cytochrome *c* accompanied by other pro-apoptotic molecules. Cytochrome *c* interacts with the cytosolic apoptotic-protease-activating factor-1 (Apaf-1) to facilitate the formation of apoptosomes and initiate the apoptotic process. In a complex with deoxyadenosine triphosphate (dATP) and cytochrome *c,* Apaf-1 activates the inactive pro-caspase-9, which in turn cleaves and activates caspase-3 [97–99]. SMAC protein leaked from mitochondria binds to X chromosome-linked inhibitor-of-apoptosis protein (XIAP) and suppresses its anti-apoptotic activity, which prevents serial procaspase activation and triggers apoptotsis after cerebral ischemia [100,101]. The mitochondrial protein AIF was identified as a caspase-independent mediator of the degradation phase of apoptosis and suggested to function as a mitochondrial effector of apoptotic cell death following translocation from mitochondria to the nucleus [102]. AIF has been shown to inhibit poly(ADP-ribose) polymerase and be retained in the nuclei by Bid, thus accelerating and strengthening the apoptotic process [103]. In an animal model of ischemic stroke, AIF translocation occurs before or at the time of cytochrome *c* release from mitochondria, and is evident in cells showing apoptotic DNA fragmentation [104]. AIF is also responsible for neuronal death caused by glutamate-induced toxicity and oxygen-glucose deprivation in vitro and experimental ischemic stroke in vivo [103].

4. Roles of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) in ROS-protective mechanisms and mitochondrial biogenesis during cerebral ischemia

In cerebral ischemia, a detrimental cascade starts with decreased cerebral blood flow, elevated glutamate release and calcium influx, and increased ROS formation, which trigger the apoptotic pathway, and ends with neuronal death [20,57]. Endogenous protectors such as inhibitor-of-apoptosis protein (IAP), peroxisome proliferator-activated receptors (PPARs), and the PI3K-Akt signaling axis may be induced that can prevent the activation of apoptotic pathways. In this section, we focus on the anti-apoptotic and protective molecules that may be utilized as targets in the development of potential treatments for cerebral ischemic stroke. We place special emphasis on PGC-1α.

IAPs are a family of proteins containing an approximately 70-amino-acid domain called baculoviral IAP repeat, which are known to function as endogenous inhibitors of apoptosis by impeding the cleavage of procaspases and suppressing active caspases intrinsically [105]. Six IAPs, including XIAP, NAIP, c-IAP1, c-IAP2, Survivin, and Livin, have been identified in humans; especially XIAP, which is the most studied IAP, binds caspase-3, caspase-7, and caspase-9 to suppress their activities and prevent apoptosis [106]. Some members of the Bcl-2 family, Bcl-2, Bcl-XL, and Bcl-w, which have also been characterized, serve to act as IAPs to repress the apoptotic process via various combinations of the Bcl-2 homologous domains BH1, BH2, BH3, and BH4 [107]. Accumulating evidence suggests that IAPs not only inhibit apoptosis but also repress necroptosis and pyroptosis [106]. The PI3K-Akt axis is a major downstream signaling pathway of several neurotrophic factors such as NGF, insulin-like growth factor 1, and BDNF, which enhances neuronal survival against stresses in response to neurotrophic factors [108]. Several survival genes such as Bcl-XL and several IAPs are regulated by CREB and nuclear factor-κB (NF-κB), the transcriptional factors of PI3K-Akt signaling cascade [109,110]. Akt has been reported to directly phosphorylate FOXOs and inhibit FOXOs to induce the expression of death genes including FasL and Bim [108]. Furthermore, Akt also phosphorylates BAD, an apoptotic protein of the Bcl-2 family, to repress BAD-induced apoptosis. Akt activity is augmented by overexpressed superoxide dismutase 1 (SOD1) to repress neuronal death during ischemic stroke [111]. PI3K-Akt signaling cascade is a potential target for the development of neuroprotective drugs for cerebral ischemic stroke. PPARs function as ligand-activated transcription factors to regulate cell proliferation and differentiation, glucose homeostasis, lipid and lipoprotein metabolism, as well as cellular apoptotic processes [112]. Notably, PPARs also regulate the inflammatory and oxidative responses [113–115]. Evidence shows that PPARs exert beneficial effects in inflammatory diseases via modulation of adhesion molecule expression and cytokine production through interfering with the transactivation capacity of signal transducers and activators of transcription (STATs), activator protein-1, and nuclear factor-κB (NF-κB) [113,116,117]. It is well known that PPARγ activation can alleviate the post-ischemic inflammatory response and damage [115,118,119]. The available evidence suggests that the anti-oxidation, anti-inflammation, and anti-apoptotic processes described above may be potentially used as therapeutic targets to ameliorate the symptoms of post-ischemic stroke. PPARγ agonists, such as pioglitazone or rosiglitazone, clinically used for diabetes, have been shown to reduce inflammation [120,121], reduce oxidative damage [61,119,120,122,123], and decrease cell death following ischemic injury. In a recent clinical trial involving patients without diabetes but with a recent history of ischemic stroke or transient ischemic attack, the outcome measurement with a risk of stroke or myocardial infarction was lower in patients administered pioglitazone as treatment than in those administered the placebo [124]. A systematic review and meta-analysis showed that pioglitazone reduces recurrent stroke and major vascular events in ischemic stroke patients with insulin resistance, prediabetes, and diabetes mellitus [125].

PGC-1α was originally identified as a cold temperature-induced protein in thermogenic brown adipose tissue and as a transcriptional coactivator that may provide critical insights for transcriptional control mechanisms with a diverse array of cellular factors that connect sequence-specific DNA binding activators to the general transcriptional machinery [126]. Studies have revealed that PGC-1α transduces multiple physiological stimuli into specific metabolic reactions such as fatty acid oxidation, gluconeogenesis, mitochondrial biogenesis, and thermogenesis [127–129]. In particular, PGC-1α is suggested to play a pivotal role in the regulation of energy metabolism in tissues/organs with high metabolic demands such as brown adipose tissue, muscle, brain, heart, kidney, and liver [24,127,130]. Several neurodegenerative diseases, such as AD, PD, and HD, have been reported to be pathogenically associated with dysfunctional mitochondria and diminished expression of mitochondrial respiratory proteins [131]. A study by Lin et al. showed that PGC-1α knockout mice develop a remarkable spongiform

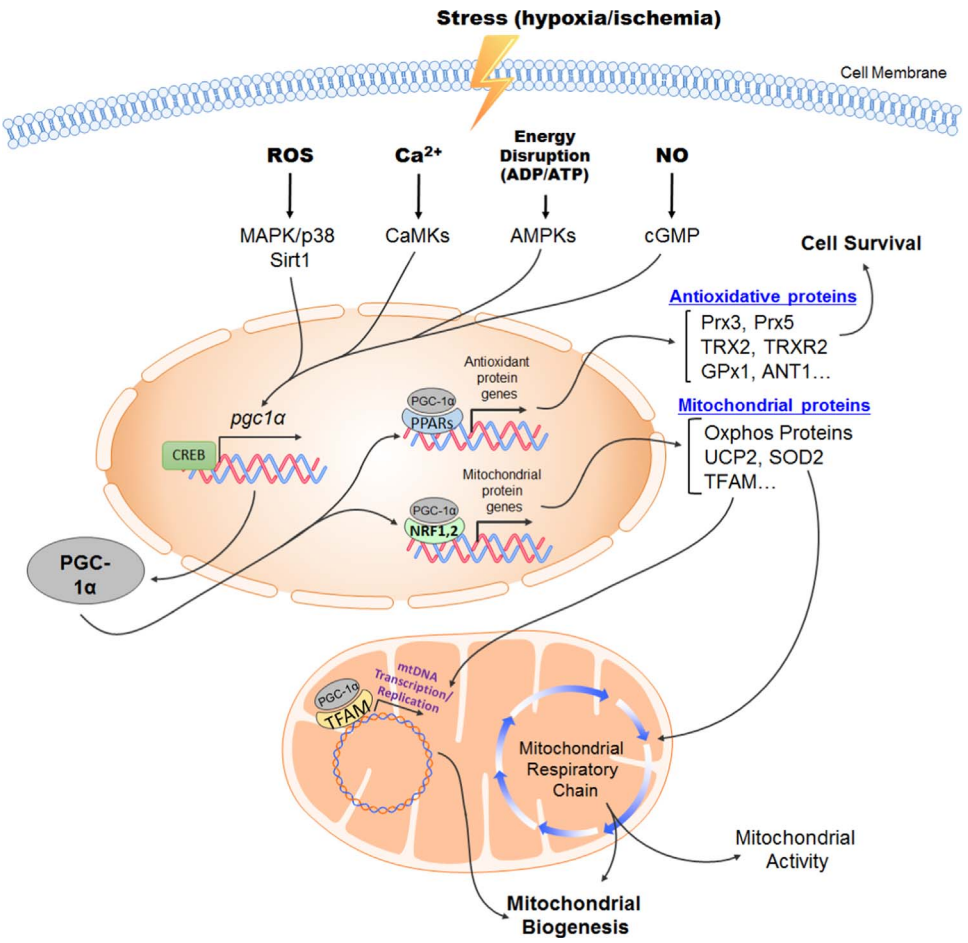

Fig. 2. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) plays a central role in protective mechanisms and mitochondrial biogenesis during hypoxia/ischemia-induced stress. Stress-induced molecules, including reactive oxygen species (ROS), Ca^{2+}, ADP/ATP, and nitric oxide (NO), trigger various signaling pathways and promote PGC-1α expression. Subsequently, PGC-1α, a well-known transcription factor, upregulates the expression of antioxidant proteins and enhances mitochondrial biogenesis to protect neurons against oxidative stress. AMPK, AMP-activated protein kinase; ANT1, adenine nucleotide translocator 1; CAMK, Ca^{2+}/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; GPx1, glutathione peroxidase 1; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NRF, nuclear respiratory factor; PPAR, peroxisome proliferator-activated receptor; Prx, peroxiredoxin; SOD2, superoxide dismutase 2; TFAM, transcription factor A, mitochondrial; TRX2, thioredoxin 2; TRXR2, thioredoxin reductase 2; UCP2, uncoupling protein 2.

lesion in the striatum, the brain area affected in HD patients, and in the hippocampus and substantia nigra, the 2 areas predominantly affected in patients suffering from AD and PD, respectively [132].

Taking all lines of evidence together, PGC-1α activation or overexpression may be a means to counteract mitochondrial dysregulation in neurons, making any agents activating PGC-1α potentially beneficial in neurodegenerative diseases in which oxidative damage and mitochondrial dysfunction play crucial pathogenic roles [133]. Several studies have shown that excessive oxidative stress and the unbalanced redox state of ischemic neurons are involved in a signaling pathway that stimulates PGC-1α expression [21,134]. PGC-1α is induced under hypoxic conditions and has been suggested to have protective functions in skeletal muscle and cerebral cortical tissues [135–137]. Enhancing PGC-1α expression rescues cultured neural cells from oxidative-stress-mediated cell death; conversely, suppressing PGC-1α expression aggravates the harmful effects of kainic acid injection in the hippocampus and those of 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine in the substantia nigra in mice [24]. Nonetheless, the exact roles of PGC-1α in ROS metabolism during cerebral ischemia remain unclear. Considering the tight relationship between ischemia-induced neuronal damage and excessive ROS production, it is highly likely that PGC-1α plays a significant protective role in the ischemic stroke paradigm.

Mitochondrial uncoupling protein 2 (UCP2) and superoxide dismutase 2 (SOD2) are 2 crucial ROS-detoxifying proteins that prevent cellular damage and neuronal death through regulation of mitochondrial ROS production [138–141]. Enhancement of UCP2 expression reduced ROS production and neuronal loss in the ischemic brain area, demonstrating distinct neuroprotective properties of UCP2 against ischemic brain injury [61,139,142]. In addition, animals overexpressing SOD2 revealed a protective effect against oxidative-stress-induced neuronal injury after transient focal cerebral ischemia [143,144]. Our previous study demonstrated that transient cerebral ischemia induced ROS overproduction, promoted activation of the PGC-1α signaling pathway, and, consequently, triggered the expression of SOD2 and UCP2 in hippocampal CA1 neurons [23]. We also applied antisense oligodeoxynucleotide to silence PGC-1α expression, resulting in decreased UCP2 and SOD2 protein levels, aggravation of oxidative damage, and increased neuronal death in the hippocampus after transient cerebral ischemia [23]. These results suggest that PGC-1α regulates UPC2 and SOD2 expression and protects neurons in cerebral ischemia. Our observations are in line with previous studies showing that PGC-1α regulates several other antioxidant proteins including catalase, adenine nucleotide translocator 1, glutathione peroxidase (GPx1), peroxiredoxins III and V, thioredoxin reductase 2, and thioredoxin 2 [24,145]. Thus, the PGC-1α signaling pathway is a promising target for neuroprotective therapeutic strategies against ischemic brain damage.

Mitochondria have distinct functions for cellular homeostasis in regulating bioenergy, biosynthesis, and signaling [146]. Leaking mitochondrial oxidants mediate cellular death/survival signaling in stress-compromised cells. However, highly active redox processes and intrinsic ROS production lead to progressive impairment and associated dynamic regulation of internal content, biological functions, and renewal of this critical intracellular organelle [147]. The dynamic regulation of mitochondria is particularly crucial for the appropriate function of post-mitotic neurons. Interestingly, regular mitochondrial biogenesis requires the coordinated production and import of an estimated 1000–1500 nuclear-genome-encoded proteins [148]. Nonetheless, the current knowledge is still limited onconcerning the cross-talk between nuclei and mitochondria in the regulation of mitochondrial biogenesis, as well as the role of the latter mitochondrial

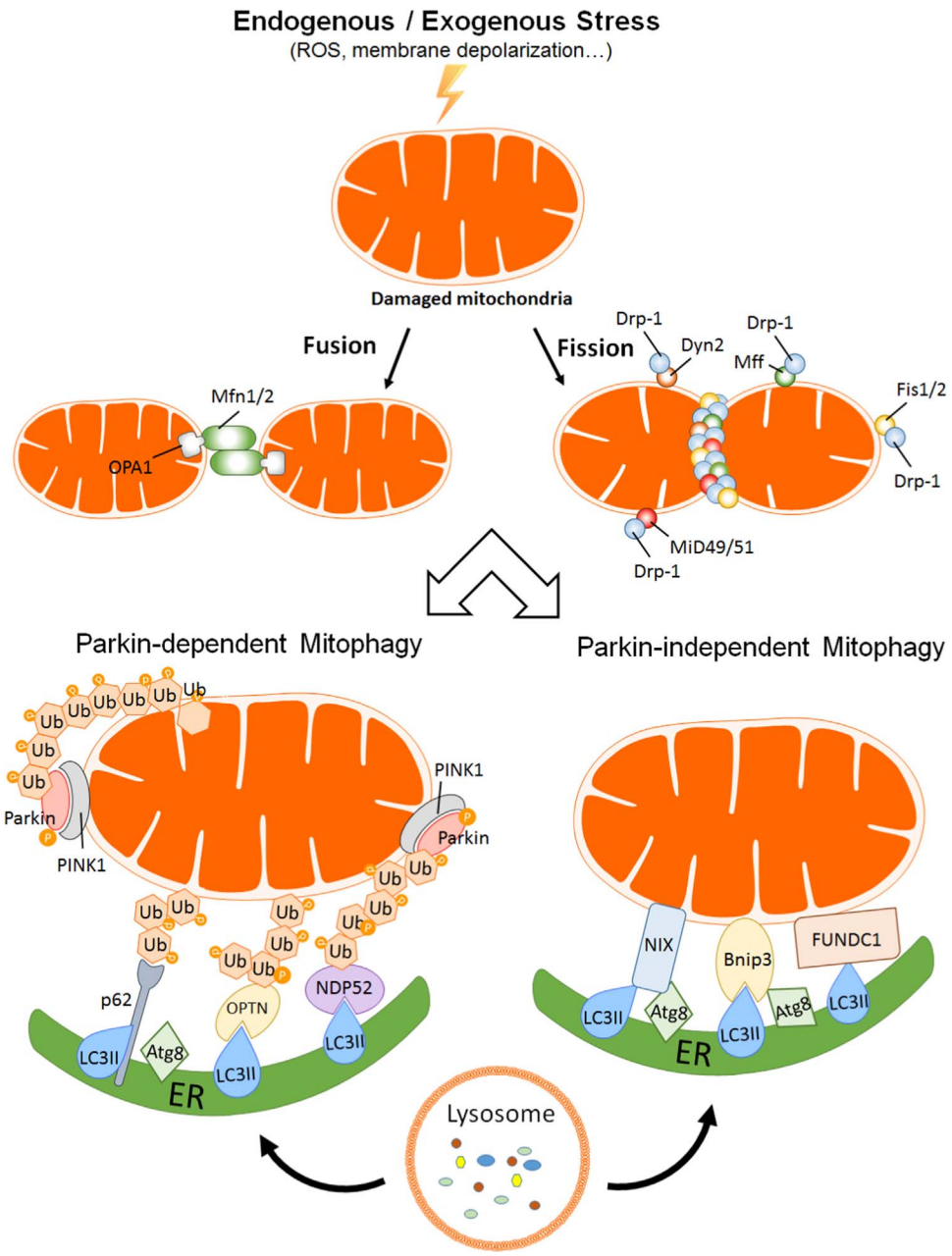

Fig. 3. Mitochondrial dynamics and mitophagy have pivotal functions in cell death and survival during cerebral ischemia. Mitochondrial dynamics (fusion/fission) and mitophagy are 2 critical cellular processes maintaining mitochondrial function and energy homeostasis. Mitochondrial fusion and fission maintain functional mitochondria while under a stress insult. However, dysfunctional or over-abundant mitochondria continuously undergo mitophagy after mitochondrial fusion of fission. The proper regulation of both mitochondrial dynamics and mitophagy helps cell survival; conversely, imbalanced mitochondrial dynamics and mitophagy or excessive insults lead to cell death. Atg8, autophagy-related protein 8; Bnip3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; Dyn, dynamin; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; Fis1/2, fission protein 1/2; FUNDC1, FUN14-domain-containing protein 1; Mff, mitochondrial fission factor; Mfn, mitofusin; MID49/51, mitochondrial dynamic protein of 49/51 kDa; NDP52, nuclear dot protein of 52 kDa; NIX, Nip3-like protein X; LC3, light chain 3; OPTN, optineurin; PINK1, phosphatase-and-tensin-homolog-induced putative kinase 1; ROS, reactive oxygen species.

biogenesis in the survival of stressed neural cells, is still limited. Mitochondrial biogenesis involves coordination of nuclear and mitochondrial gene expression, in which the transcriptional coactivator PGC-1α may be a key player. PGC-1α has often been suggested to be a critical regulator of mitochondrial biogenesis under hypoxic-ischemic conditions via directly or indirectly upregulating several mitochondrion-related proteins, including cytochrome *c* oxidase IV, nuclear respiratory factor 1(NRF-1), and mitochondrial transcription factor A (TFAM) [25,149–152]. TFAM binds the D-loop region of mitochondrial DNA (mtDNA) and directs the replication and transcription of the mitochondrial genome [152]. The TFAM gene contains consensus binding sequences for both NRF-1 and NRF-2, while PGC-1α and NRFs (1 or 2) synergistically regulate mitochondrial biogenesis by incorporating both nuclear- and mitochondrial-encoded proteins [150,152] (Fig. 2).

Mitochondria act as cell energy centers and respond to changes in cellular homeostasis; therefore, exploring the roles of mitochondrial biogenesis into ischemic injury may contribute to the development of strategies to augment this beneficial effect and ameliorate the ischemic-related detrimental consequences of ischemia. Our previous studies have shown that the PGC-1α signaling pathway is activated in transient global ischemia and triggers mitochondrial biogenesis in the hippocampal CA1 area, in agreement with mitochondrial biogenesis exerting a protective effect by enhancing signal transduction pathways upstream of mitochondrial biogenesis [23,25,153]. A limited number of chemicals are known to enhance mitochondrial biogenesis via various pathways. For example, agonists of the β-adrenergic receptors and G protein–coupled serotonin receptors can trigger the protein kinase B/eNOS synthase/cGMP pathway to boost mitochondrial biogenesis [154,155]. NO donors and phosphodiesterase inhibitors increase cGMP and cAMP via precluding the hydrolyzation of cGMP and cAMP to elevate PGC-1α and stimulate mitochondrial biogenesis [156,157]. We have shown that the CaMKIV/PGC-1α pathway implicates mitochondrial biogenesis in ischemic brain injury [23]. It was reported that PPARγ agonist can upregulate PGC-1α, NRF1, TFAM, and cytochrome c oxidase subunit I and IV, and enhance mitochondrial biogenesis [158]. Moreover, resveratrol, a polyphenol with pleiotropic effects that can stimulate mitochondrial

biogenesis through the sirtuin 1 pathway to catalyze PGC-1α deacetylation, is under investigation for the treatment of a variety of neurodegenerative diseases [159,160]. It was noted that these signaling pathways can converge to activate PGC-1α and increase mitochondrial biogenesis [161,162]. Several articles on the pharmacological approach to enhance mitochondrial biogenesis are well reviewed elsewhere [156,157,163,164]. The PGC-1α signaling cascade may be an innovative target for a therapeutic approach to ischemic brain damage treatment.

5. Mitochondrial dynamics in cell death and survival during cerebral ischemia

Mitochondria were first described as “bioblasts” by Altmann in 1890, followed by Benda's 1898 observation of their miscellaneous morphology, sometimes ball-shaped and other times elongated, which inspired the name mitochondrion, based on the Greek words “mitos” (thread) and “chondrion” (granule) [165,166]. Accumulating evidence suggests that mitochondrial dynamics, characterized by radical morphological transformation, is intimately involved in apoptosis under stressful conditions [167,168]. Mitochondria uphold their shape and morphology through 2 opposing processes, fission and fusion, under various conditions [26–28]. The fission process involves constriction and cleavage, whereas fusion tethers and joins 2 adjacent mitochondria [26–28]. In the initial step of mitochondrial fission, endoplasmic reticulum (ER)-localized inverted formin 2 mediates interaction between the ER and actin to create constriction sites before mitochondrial dynamin-related protein1 (Drp1) recruitment [169,170]. Drp1, a key regulator of fission, is recruited from the cytosol to the outer mitochondrial membrane by several receptor proteins including mitochondrial fission protein (Fis1), mitochondrial dynamics proteins of 49 and 51 kDa, and mitochondrial fission factor. Dynamin 2 then acts in concert with Drp1 to form a ring-like structure through oligomerization and split the mitochondrial membrane by GTP hydrolysis and self-assembly in the final step of fission [171–175] (Fig. 3). Studies have reported that mitochondria disintegrate into multiple small units by fission just before apoptosis, and preventing mitochondrial fission can block cytochrome *c* release and delay cell death [168]. Mitochondrial oxidative stress has been suggested to upregulate Drp1 expression and lead to an imbalance of mitochondrial fission and fusion, resulting in mitochondrial fragmentation and dysfunction, and cell death [176]. Antioxidants such as vitamin E or MitoQ can reduce mitochondrial fragmentation and Drp1 expression [177,178]. In turn, Drp1 knockdown decreases mitochondrial ROS production and oxidative stress [179–181]. Drp1 has been suggested to play a crucial role in focal cerebral ischemia, and downregulation of the Drp1 protein levels reduces the infarct volume [30–32]. *In vitro* studies have demonstrated that mitochondrial fragmentation and apoptotic cell death are significantly decreased in dominant-negative Drp1 mutant cell lines in response to a variety of insults [182,183]. Thus, Drp1 is critical not only for mitochondrial fission but also for cell fate. In mitochondrial fusion, both the inner and outer membranes are regulated by several large GTPase proteins, including optic atrophy protein 1 (Opa1; inner membrane) and mitofusins 1 and 2 (Mfn1 and 2; outer membrane) [184] (Fig. 3). In normal conditions, mitochondrial fusion augments mitochondrial integrity by allowing component distribution and sharing across the tubular network [185]. Defects in the mitochondrial fusion process may lead to neurodegenerative disorders such as Charcot-Marie-Tooth neuropathy [186,187]. Mitochondrial fusion proteins including Mfn1, Mfn2, and Opa1 are less studied in cerebral ischemia [188–191]. It was revealed that in vivo and in vitro hypoxic models decreased Mfn2 expression, and Mfn2 may exert anti-apoptotic effect via restoration of mitochondrial function [188,189]. It was reported that exercise can increase the expression of Opa1 and alleviate brain edema in cerebral ischemic injury [190] and inhibition Opa1 and Mfn2 in ischemic conditions can be further compromised by hyperglycemia [191]. The potential beneficial effect of mitochondrial fusion, especially enhancement of Mfn2 expression, in cerebral ischemia remains to be elucidated. Signaling lipids such as cardiolipin, diacylglycerol, lysophosphatidic acid, phosphatidylethanolamine, phosphatidic acid, as well as their synthases and metabolic enzymes, were also found to be involved in the control of mitochondrial fission and fusion [192].

Mitochondrial dynamics is important for the regulation of cell survival and death; particularly, mitochondrial fission is an early upstream event in neuronal death after cerebral ischemia [30–32]. Recently, we have shown that transient global ischemia induces a brief increase in p-Drp1(Ser616) in the rat hippocampal CA1 region [33]. This finding strengthens the case for a critical role of mitochondrial dynamics in ischemia-induced neuronal death. Mitochondria play a major role in the regulation of cell destiny in various diseases including cerebral ischemia. Mitochondria control cell survival through the production of ATP, which energizes cellular processes and induces apoptosis. The release of pro-apoptotic factors such as AIF, cytochrome *c,* endonuclease G, mitochondrial serine protease HtrA2/Omi, and SMAC/DIABLO mediates apoptosis initiation by ATP [193,194]. Thus, stringent quality control mechanisms are critical to maintain a healthy mitochondrial network. Such mechanisms include mitochondrial dynamics and mitophagy [195].

6. Critical role of mitophagy in cerebral ischemia

Autophagy is an evolutionarily conserved process by which lysosomes degrade unnecessary or dysfunctional cellular proteins and organelles. During autophagy, redundant or impaired cellular components are engulfed by a double-membraned vesicle known as an autophagosome. The autophagosome then fuses with a lysosome, which leads to the degradation and recycling of the components from dysfunctional organelles and proteins [196]. Three distinct subtypes of autophagy are generally recognized in mammalian cells: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy is the major and best-studied mechanism of degradation and recycling of cellular components, usually termed “autophagy”. Autophagy is assumed to be relatively non-selective toward its substrates [197,198]. Autophagy has also been found to be involved in the maintenance of intracellular homeostasis through selective degradation of cellular content such as misfolded, aggregated, or overabundant proteins, damaged organelles, excess peroxisomes, and invading pathogens in non-starved cells [199–201]. Autophagy is critical for cell and tissue homeostasis and involved in the natural course of aging as well as various human disorders, including cancer, compromised innate immunity, muscular dystrophy, and neurodegeneration [37]. The process of autophagy can be triggered by cerebral ischemia both in vitro [202] and in vivo [203]. Autophagy is a double-edged sword: it can be detrimental [204] or protective [205]. What determines which edge is used remains unclear. Nevertheless, autophagy may be a useful target of treatment if its protective effect can be regulated.

Mitochondria have been implicated in various crucial functions such as cell cycle and growth control, differentiation, signaling, and cell death. Impaired mitochondrial functions have been linked to several diseases, including diabetes, heart failure, innate immunity deficiencies, and neurological defects [37]. Hence, maintaining the quality and function of mitochondria is pivotal for cell survival and health. Mitophagy is one of the best-studied types of selective autophagy crucial for supporting mitochondrial homeostasis by eliminating impaired mitochondria. We will summarize the current knowledge on mitophagy regulation in cerebral ischemia and discuss the molecular mechanisms and pathophysiological roles of mitophagy in ischemic brain injury.

In mammalian cells, 2 signaling routes exist related to the mechanisms of mitophagy regulation, the phosphatase-and-tensin-homolog-induced putative kinase 1 (PINK1)/parkin-dependent

pathway [206] and PINK1/parkin-independent pathway [207] (Fig. 3). Reduction in the mitochondrial membrane potential activates the parkin-dependent mitophagy pathway, including excessive Ca^{2+} influx or inhibitors/uncouplers of the mitochondrial respiration chain [208]. Damaged mitochondria with a compromised membrane potential show impaired PINK1 cleavage and maintain steady PINK1 activity. Active PINK1 recruits cytosolic parkin to damaged mitochondria through phosphorylation of both parkin and ubiquitin at Ser 65 residues to initiate PINK1/parkin-dependent mitophagy. Parkin, a E3 ubiquitin ligase, ubiquitylates outer mitochondrial membrane substrates and adaptor proteins, such as sequestosome-1 (p62), nuclear dot protein of 52 kDa, and optineurin [209]. The ubiquitylated adaptor proteins bind microtubule-associated protein light chain 3 (LC3) and the ER membrane to form an autophagosome. Consequently, the mitochondria are closed up by the ER isolation membranes and fuse with lysosomes in the process of degradation.

In parkin-independent mitophagy, the mitochondrial receptor Nip3-like protein X (NIX, a BH3-only Bcl-2 family protein), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (Bnip3), and FUN14-domain-containing protein 1 (FUNDC1) are among the most important. Under hypoxia or starvation, the expression of NIX and Bnip3 is upregulated, promoting mitophagy [210,211]. The WXXL-like motif of NIX and Bnip3 is exposed to the cytosol and binds to autophagy-related protein 8 (Atg8) and LC3, thus facilitating mitophagy. FUNDC1, another outer mitochondrial membrane protein, includes a typical LC3-interacting region that can bind LC3II or Atg8 to induce mitophagy as well [212] (Fig. 3).

During cerebral ischemia, hypoxia enhances Bnip3 and NIX expression, triggers the liberation of beclin-1 from the Bcl-2/beclin-1 complex, and ultimately induces mitophagy [213]. Spontaneous or treatment-induced reperfusion is encountered often after cerebral ischemia. Post-ischemic reperfusion is usually accompanied by a surge in ROS levels that disrupts the mitochondrial membrane potential and results in the translocation of parkin from the cytosol to the impaired mitochondria, facilitating mitophagy. The pivotal roles of mitochondrial dynamics and fission in promoting neuronal death after cerebral ischemia were discussed in Section 5. Mitochondrial fusion is enhanced by elevated Drp1 and Fis1, and decreased Opa1 and Mfn2 expression [30]. Excessive mitochondrial fission can cause mitochondrial fragmentation, which is a critical step in the process of mitophagy leading to cell death [31,32]. Some studies have also demonstrated that rapamycin treatment increases the protein levels of beclin-1, PINK1 and LC3II, promotes the translocation of p62 to damaged mitochondria, and exerts neuroprotective effects by enhancing autophagy and mitophagy [214,215]. However, mitophagy is also a double-edged sword for cell survival: either insufficient removal of damaged mitochondria or unwarranted degradation of functional mitochondria will result in cell death. Given the binary role of “life-or-death” adherence to mitochondria, in concert with the evident connection among mitophagic proteins, mitochondrial dynamic proteins, and apoptotic proteins, lead to the question of whether mitophagy is advantageous or harmful to cell destiny in response to I/R injury [195]. The underlying pathogenesis of mitophagy in cerebral ischemia and the potential of exogenous manipulation, such as a pharmacological approach to enhance the beneficial aspects of mitophagy, remain to be further elucidated and clarified.

7. Emerging roles of mitochondria in immunity in cerebral ischemia

The endosymbiotic hypothesis of mitochondrial origin posits that mitochondria initially were prokaryotic cells residing in eukaryotic organisms, becoming intracellular symbiotic organelles during biological evolution [216]. Therefore, mitochondria still retain features of their bacterial ancestry that can trigger inflammatory responses via the innate and adaptive immune pathways [217,218]. Mitochondrial antiviral-signaling protein (MAVS) activates the transcription factor NF-κB and interferon regulatory factors to promote inflammatory-related gene expression via the retinoic-acid-inducible gene-1 (RIG-1), encoding a viral RNA receptor, and interaction with the outer mitochondrial membrane [219]. Virus-independent MAVS oligomerization was demonstrated in patients with systemic lupus erythematosus. Mitochondrial ROS (mtROS) might be a critical sensor to enhance host defense and inflammation [220]. However, accumulating evidence supports mitochondria playing a new role in innate immunity.

MtDNA acts as a danger-associated molecular pattern. The outer mitochondrial membrane serves as a platform for the assembly of the inflammasome; MAVS, RIG-1, and the NLRP3 inflammasome are the main players in the mitochondrion-induced inflammatory response [221]. MtDNA is a circular loop that contains numerous C*p*G islands. Stress, injury, or necrosis may cause mtDNA fragmentation, resulting in fragmented mtDNA being released into the cytosol and activating toll-like receptor 9 (TLR9), a C*p*G DNA receptor [222,223]. Activated TLR9 triggers the NF-κB signaling pathway and induces multiple genes coding for proinflammatory proteins such as tumor necrosis factor-α and IL-6 [224]. Moreover, fragmented mtDNA can also lead to the activation of the NLRP3 inflammasome [225], which induces caspase-1 to cleave pro-IL-1β and pro-IL-18, eventually resulting in pyroptotic cell death [226]. Furthermore, mitochondrial dysfunction due to excessive oxidative stress also elicits NLRP3 oligomerization or induces α-tubulin acetylation to bring mitochondria to the proximity of NLRP3 [227]. MtROS augment the effect of mtDNA on NLRP3 activation as well as the downstream processes [225,228]. MtROS upregulation may therefore function as an important trigger of NLRP3 inflammasome activation [229] (Fig. 4).

The inflammatory process is involved in all stages of the ischemic cascade, from the earliest cerebral arterial occlusion to late recovery phases. The inflammatory response includes both the innate and adaptive immune-cell reactions, which potentially offers the opportunity for an innovative therapeutic approach [44,230]. Following acute brain ischemia, activated microglia release proinflammatory cytokines, leading to neuronal cell death [231]. Consistent with these observations, NLRP3 protein levels were found to increase after ischemic stroke concurrently with elevated IL-1β and IL-18 expression and wide-ranging glial and neuronal death [232,233] (Fig. 4). By comparing NLRP3(-/-) and wild-type ischemic stroke mice, these studies demonstrated reduced blood-brain barrier damage and decreased infarct size in NLRP3-deficient animals; the protective effect was associated with reductions in the NLRP3-mediated IL-1β release, brain microvessel endothelial cell permeability, and microglia-mediated neurotoxicity [234]. Similarly, another study showed that NLRP1 and NLRP3 inflammasome activity was suppressed by intravenous immunoglobulin (IVIg) treatment, reducing neuronal death and behavioral deficits in ischemic stroke mice [232]. Recently, Fann et al. reported that activation of either the p38/mitogen-activated protein kinase or NF-κB signaling pathway was partially responsible for the production of NLRP1 and NLRP3 inflammasome proteins, and this effect could be impeded by IVIg to inhibit the 2 pathways under both in vitro and in vivo ischemic conditions [235] (Fig. 4). Taken together, these results suggest that downregulation of NLRP3 activation can improve the outcomes of cerebral ischemia, as shown by reductions in the infarction volume and neurovascular damage. All lines of evidence indicate that the NLRP3 inflammasome plays a vital role in glial and neuronal cell death in ischemic stroke, and blocking NLRP3 inflammasome activity is an innovative therapeutic approach for ischemic stroke.

8. Conclusion

Many earlier studies of mitochondria were mostly focused on their bioenergetic role; however, in recent decades, thanks to advancements in animal models, imaging techniques, and systems-based approaches, our view of mitochondria has been swiftly changing. We have

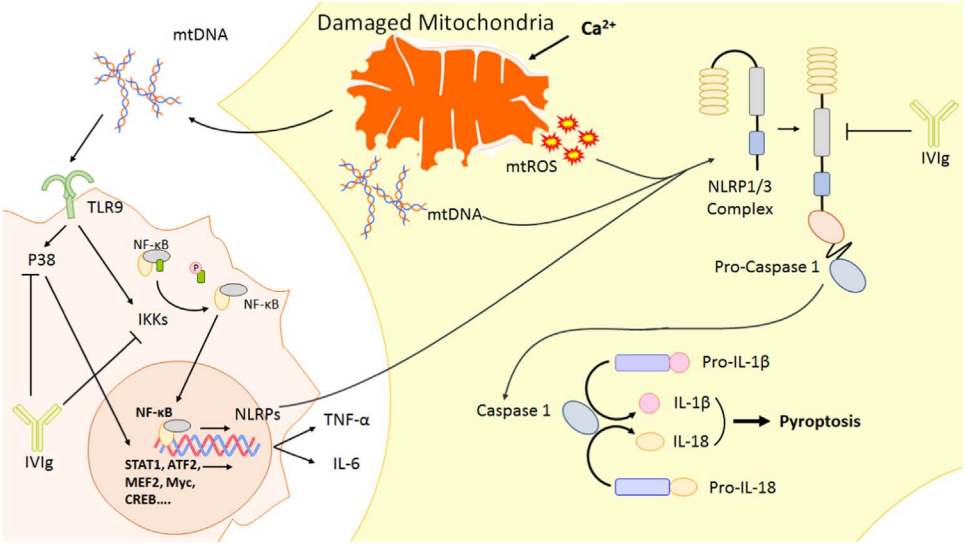

Fig. 4. Mitochondrion-triggered signaling pathways involved in the innate immune response in cerebral ischemic stroke. Mitochondrial reactive oxygen species (mtROS) and DNA (mtDNA) play important roles in triggering the innate immune response via the NLR family pyrin-domain-containing protein 1/3 (NLRP1/3) and p38/NF-κB signaling pathways, respectively. MtROS acts as a critical sensor of inflammation and activates the NLRP1 and NLRP3 inflammasomes, which in turn induces caspase-1 to cleave pro-interleukin (IL)-1β and pro-IL-18, culminating in pyroptotic cell death. Fragmented mtDNA can also be released into the cytosol and activate toll-like receptor 9 (TLR9), triggering the p38 or NF-κB signaling pathways and inducing tumor necrosis factor-α (TNF-α), IL-6, and NLRP1/3 expression. Intravenous immunoglobulin (IVIg) treatment reduces the protein levels of NLRP1 and NLRP3 and inhibits p38 and NF-κB activities, suppressing the downstream inflammatory response. ATF2, activating transcription factor 2; CREB, cAMP response element-binding protein; IKK, IκB kinase; MEF2, myocyte enhancer factor-2; NF-κB, nuclear factor-κB; STAT1, signal transducer and activator of transcription 1.

witnessed the appreciation of the significance of these organelles in a wide range of cellular functions and signaling events. These include functions involved in cerebrovascular disease, such as apoptotic signaling, mitochondrial biogenesis, mitochondrial dynamics, mitophagy and quality control, and an emerging role in immunity. Stroke is a leading cause of mortality and mobility in modern society, both in developed and developing countries. Limited treatment options currently exist, only for a small proportion of stroke victims, making it vital to develop effective treatments reducing brain impairment based on an understanding of the pathogenic molecular mechanisms underlying ischemic insults. Characterization of mitochondrial protective mechanisms may provide a rationale for the development of new therapeutic regimens for ischemic stroke.

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Author contributions

Jenq-Lin Yang contributed to concept generation and the drafting of the manuscript. Sujira Mukda contributed the mitochondria and inflammation part of the manuscript. Shang-Der Chen contributed to concept generation. All authors approved the article.

Conflicts of interest

The authors declare no conflicts of interest.

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