Diverse roles of mitochondria in ischemic stroke

Jenq-Lin Yang, Sujira Mukda, Shang-Der Chen

Review article

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 often overlooked as a potential therapeutic target. Mitochondria 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 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

ARTICLE INFO

Keywords:
Mitochondria
Ischemic stroke
Apoptosis
Mitochondrial biogenesis
Mitochondrial dynamics
Mitophagy
Inflammation

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 often overlooked as a potential therapeutic target. Mitochondria 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.
synthase 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 mitochondriald 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 bc1 complex III, and cytochrome c oxidase complex IV, which together produce a proton motive force that drives ATP generation by complex IV (F1F0-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 (QH2). Complex II (succinate–quinnon oxidoreductase) offers an additional entrance point for electrons of QH2 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 process 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 as 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 (NLPR3) 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 NLPR3 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 enzymatic 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
J.-L. Yang et al.

Redox Biology 16 (2018) 263–275

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, 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 (MTPs) in the mitochondrial inner membrane [96]. A transient opening of MTPs 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 apoptosisomes 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 apoptosis 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 PPARα 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. PPARα 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
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 over-expression 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 UCP2 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 1, MAPK, mitogen-activated receptor; Prx, peroxiredoxin; SOD2, superoxide dismutase 2; TFAM, transcription factor A, mitochondrial; TRX2, thioredoxin 2; TRXR2, thioredoxin reductase 2; UCP2, uncoupling protein 2.

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), Ca2+, 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, Ca2+/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.
Mitochondrial 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 mitochondrial-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 up-regulate 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

**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 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 Altman 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 2 mediates interaction between the ER and actin to create constriction sites before mitochondrial dynamin-related protein 1 (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 factor (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. Macropathology 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
mitophagy in cerebral ischemia and the potential of exogenous ma-
exerts neuroprotective e 
the question of whether mitophagy is advantageous or harmful to cell 
teins, mitochondrial dynamic proteins, and apoptotic proteins, lead to 
dria, in concert with the evident connection among mitophagic pro-
survival: either insu 
mitochondrial membrane protein, includes a typical LC3-interacting 
8 (Atg8) and LC3, thus facilitating mitophagy. FUNDC1, another outer 
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 ex-
pression, 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 mitochon-
drial 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 frag-
mentation, which is a critical step in the process of mitophagy leading 
to cell death [31,32]. Some studies have also demonstrated that rapa-
mycin 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 
warranted degradation of functional mitochondria will result in cell 
death. Given the binary role of “life-or-death” adherence to mitochon-
dria, in concert with the evident connection among mitochondrial pro-
teins, mitochondrial dynamic proteins, and apoptotic proteins, lead to 
the question of whether mitophagy is advantageous or harmful to cell 
density in response to I/R injury [195]. The underlying pathogenesis 
of mitophagy in cerebral ischemia and the potential of exogenous ma-
nipulation, such as a pharmacological approach to enhance the bene-
ficial aspects of mitophagy, remain to be further elucidated and clar-
ified.

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 
or ganisms, becoming intracellular symbiotic organelles during biolo-
gical 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-re-
lated gene expression via the retinoic-acid-inducible gene-1 (RIG-1), 
encoding a viral RNA receptor, and interaction with the outer mito-
chondrial membrane [219]. Virus-independent MAVS oligomeriza-
tion 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 mitochondrial-induced inflammatory response 
[221]. MtDNA is a circular loop that contains numerous CpG 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 CpG 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 oxi-
dative 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 [225,226]. 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 opportu-
nity 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 observa-
tions, NLRP3 protein levels were found to increase after ischemic stroke 
counteractively with elevated IL-1β and IL-18 expression and wide-ran-
ging glial and neuronal death [232,233] (Fig. 4). By comparing 
NLRP3(-/-) and wild-type ischemic stroke mice, these studies demon-
strated 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 in-
flammasome activity was suppressed by intravenous immunoglobulin 
(IgV) treatment, reducing neuronal death and behavioral deficits in 
ischemic stroke mice [232]. Recently, Fann et al. reported that acti-
vation 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 IVg 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
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 injuries. Characterization of mitochondrial protective mechanisms may provide a rationale for the development of new therapeutic regimens for ischemic stroke.

Acknowledgments

This work was supported by grants CMRPG8E0761, CMRPG8F1892 and CMRPG8F1512 from the Chang Gung Medical Foundation, 106-2314-B-182-031 from the Ministry of Science and Technology, Taiwan, RSA9880041 from Thailand Research Fund, and a Mahidol University Research Grant.

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.

References

[1] F.L. Heicho, I.M. Lin, S.T. Chen, C.H. Bai, M.C. Sun, H.P. Toeng, Y.W. Chen, C.H. Chen, J.S. Jeng, S.Y. Tsai, et al., Get with the guidelines-stroke performance indicators: surveillance of stroke care in the taiwan stroke registry: get with the guidelines-stroke in Taiwan, Circulation 122 (2010) 1116–1123.
[2] L.H. Schwamm, G.C. Fonarow, M.J. Reeves, W. Pan, M.R. Frankel, E.E. Smith, G. Ellrod, C.P. Cannon, L. Liang, E. Peterson, et al., Get with the guidelines-stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack, Circulation 119 (2009) 107–115.
[3] D. National Institute of Neurological, P.A; S.S.G. Stroke rt, Tissue plasminogen activator for acute ischemic stroke, N. Engl. J. Med. 333 (1995) 1581–1587.
[4] E.C. Jauch, J.L. Saver, H.P. Adams Jr, A. Bruno, J.J. Connors, B.M. Demaerschalk, P. Khatri, P.W. McMullan Jr, A.J. Qureshi, K. Rosenfield, et al., Guidelines for the early management of patients with acute ischemic stroke: a guideline for health care professionals from the american heart association/american stroke association, Stroke 44 (2013) 870–947.
[5] M.J. Reeves, S. Arora, J.P. Broderick, M. Frankel, J.P. Heinrich, S. Hickenbottom, et al., Guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: A guideline for healthcare professionals from the American heart association/american stroke association, Stroke 2015 (2015) 3020–3035.
[6] O.A. Berkhemer, P.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J. Wijnen, et al., A randomized trial of intraarterial treatment for acute ischemic stroke, N. Engl. J. Med. 372 (2015) 11–20.
[7] M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, D. Roy, T.G. Jovin, R.A. Willinsky, B.I. Sapkota, et al., Randomized assessment of rapid endovascular treatment of ischemic stroke, N. Engl. J. Med. 372 (2015) 1019–1030.
[8] B.C. Campbell, P.J. Mitchell, T.J. Kleining, H.M. Dewey, L. Churilov, N. Yassi, B. Yan, R.J. Dowling, M.W. Parsons, T.J. Oxley, et al., Endovascular therapy for ischemic stroke with perfusion-imaging selection, N. Engl. J. Med. 372 (2015) 1009–1018.
[9] J.L. Saver, M. Goyal, A. Bonafe, H.C. Diener, E.I. Levy, V.M. Pereira, G.W. Albers, C. Cognard, D.J. Cohen, W. Hacke, et al., Stent-retriever thrombectomy after intravenous t-pa vs. t-pa alone in stroke, N. Engl. J. Med. 372 (2015) 2285–2295.
[10] T.G. Jovin, A. Chamorro, E. Colbo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilera, M. Ribo, et al., Thrombectomy within 8h after symptom onset in ischemic stroke, N. Engl. J. Med. 372 (2015) 2296–2306.
[11] Y. Hatefi, The mitochondrial electron transport and oxidative phosphorylation system, Annu. Rev. Biochem. 54 (1985) 1015–1069.
[12] L.A. Sazanov, A giant molecular proton pump: structure and mechanism of respiratory complex i, Nat. Rev. Mol. Cell Biol. 15 (2014) 375–388.
[13] A. Ames 3rd, Cnx energy metabolism as related to function, Brain Res. Brain Res. Rev. 34 (2000) 42–68.
[14] J.L. Franklin, Redox regulation of the intrinsic pathway in neuronal apoptosis, Antioxid. Redox Signal. 14 (2011) 1437–1448.
[15] K. Niihama, H. Yoshio, H. Ch, G.S. Kim, J.E. Jung, M. Katsu, N. Okami, P.H. Chan, Mitochondrial and apoptotic neuronal death signaling pathways in cerebral ischemia, Biochim. Biophys. Acts 1802 (2010) 92–99.
[16] M.T. Lin, M.F. Beal, Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases, Nature 443 (2006) 787–795.
[17] E. Cadenas, K.I. Davies, Mitochondrial free radical generation, oxidative stress, and aging, Free Radic. Biol. Med. 29 (2000) 222–230.
[18] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (2007) 44–84.
[19] S.D. Chen, J.M. Lee, D.I. Yang, A. Nassief, C.Y. Hsu, Combination therapy for ischemic stroke or transient ischemic attack, Circulation 119 (2009) 107–115.
[20] S.D. Chen, J.K. Davies, Mitochondrial free radical generation, oxidative stress, and aging, Free Radic. Biol. Med. 29 (2000) 222–230.
[21] E. Cadenas, K.I. Davies, Mitochondrial free radical generation, oxidative stress, and aging, Free Radic. Biol. Med. 29 (2000) 222–230.
[22] S.D. Chen, J.K. Davies, Mitochondrial free radical generation, oxidative stress, and aging, Free Radic. Biol. Med. 29 (2000) 222–230.
coactivator-1α against neuronal cell death in the hippocampal ca1 subfield after transient global ischemia, J. Neurosci. Res. 88 (2010) 605–613.

K. Nizuma, H. Endo, C. Nito, D.J. Myer, P.H. Chan, Potential role of pum-2 in delayed death of hippocampal ca1 neurons after transient global cerebral ischemia, Stroke 41 (2010) 618–625.

S.D. Chen, T.K. Lin, J.W. Lin, D.I. Yang, S.Y. Lee, F.Z. Shaw, C.W. Liou, Y.C. Chuang, Activation of calcium/calmodulin-dependent protein kinase iv and peroxisome proliferator-activated receptor gamma coactivator-1α signaling pathway protects against neuronal injury and promotes mitochrondrial biogenesis in the hippocampal ca1 subfield after transient global ischemia, J. Neurosci. Res. 88 (2010) 3144–3154.

J. St-Pierre, S. Drori, M. Uldry, C.M. Silvaggi, J. Rhee, S. Jager, C. Handschin, W. Yin, A.P. Signore, M. Iwai, G. Cao, Y. Gao, J. Chen, Rapidly increased neuronal mitochondrial biogenesis after hypoxic ischemic brain injury, Stroke 39 (2008) 3057–3063.

D.C. Chan, Mitochondrial fusion and fission in mammals, Annu. Rev. Cell Dev. Biol. 22 (2006) 79–99.

B. Westermann, Molecular machinery of mitochrondrial fusion and fission, J. Biol. Chem. 283 (2008) 13501–13505.

O. Kamoto, J.M. Shaw, Mitochondrial morphology and dynamics in yeast and multicellular eukaryotes, Annu. Rev. Genet. 39 (2005) 563–597.

P. Huang, C.A. Galloway, Y. Yoon, Control of mitochondrial morphology through differential interactions of mitochondrial fusion and fission proteins, PLoS One 6 (2011) e20655.

M.J. Baroum, H. Yuan, A.A. Gerencser, G. Liot, Y. Kushnareva, S. Graber, I. Kovacs, W.D. Lee, J. Waggoner, J. Cui, et al., Nitric oxide-induced mitochondrial fission is regulated by dynamin-related GTPases in neurons, EMBO J. 25 (2006) 3990–3911.

J. Groh, S.W. Kim, U. Mannik, S. Tobaben, A. Cassidy-Stone, J. Nunnari, N. Plesnila, C. Calasmes, Inhibition of drp1 provides neuroprotection in vitro and in vivo, Cell Death Differ. 19 (2012) 1446–1458.

Y.K. Zhao, M. Cai, S.F. Chen, Q. Dong, X.Y. Liu, Amelioration of ischemic mitochondrial injury and bar-dependent outer membrane permeabilization by mdivi-1, CNS Neurosci. Ther. 20 (2014) 528–538.

S.D. Chen, T.K. Lin, D.I. Yang, S.Y. Lee, F.Z. Shaw, C.W. Liou, Y.C. Chuang, Roles of PTEN-induced putative kinase 1 and dynamin-related protein 1 in transient global ischemia-induced hippocampal neuronal injury, Biochem. Biophys. Res. Commun. 460 (2015) 397–403.

N. Zhang, S. Wang, Y. Li, L. Che, Q. Zhao, A selective inhibitor of drp1, mdivi-1, acts against cerebral ischemia/reperfusion injury via an anti-apoptotic pathway in rats, Neurosci. Lett. 535 (2013) 104–109.

D.J. Klionsky, Autophagy revisited: a conversation with Christian de Duve, Science 306 (2004) 990–997.

M.A. Moskowitz, E.H. Lo, C. Iadecola, The changing landscape of ischaemic brain injury mechanisms, Nature 499 (2013) 47–54.

P. Lipton, Ischemic cell death in brain neurons, Physiol. Rev. 79 (1999) 1431–1568.

M.A. Moskowitz, E.H. Lo, C. Iadecola, The science of stroke: mechanisms in search of treatments, Neurology 70 (2008) 186–198.

H. Chen, H. Yoshio, G.S. Kim, J.E. Jung, N. Okami, H. Sakata, C.M. Maier, P. Narasimhan, C.E. Goeders, P.H. Chan, Oxidative stress in ischemic brain damage: mechanisms of cell death and potential molecular targets for neuroprotection. Antioxid. Redox Signaling 15 (2011) 1505–1517.

S.V. Lennon, S.J. Martin, T.G. Cotter, Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli, Cell Prog. 24 (1991) 203–214.

S.D. Chen, H.Y. Wu, D.I. Yang, S.Y. Lee, F.Z. Shaw, T.K. Lin, C.W. Liou, Y.C. Chuang, Effects of rosiglitazone on global ischemia-induced hippocampal injury and expression of mitochondrial uncoupling protein 2, Biochem. Biophys. Res. Commun. 351 (2006) 198–203.

E. Novo, M. Parodi, Redox mechanisms in hepatic chronic wound healing and fibrogenesis, Fibrosis. Tissue Repair 1 (2008) S.

H. Bayir, V.E. Kagan, Bench-to-bedside review: mitochondrial stress and apoptosis—there is nothing more practical than a good theory, Crit. Care 12 (2008) 206.

T. Finkel, N.J. Holbrook, Oxidants, oxidative stress and the biology of ageing, Nature 408 (2000) 239–247.

A. Kunz, L. Park, T. Abe, E.F. Gallo, J. Arauzh, P. Zhou, C. Iadecola, Neurovascular protection by ischemic tolerance: role of nitric oxide and reactive oxygen species, J. Neurosci. 27 (2007) 7083–7093.

R.S. Bablan, S. Nemoto, T. Finkel, Mitochondria, oxidants, and aging, Cell 120 (2005) 999–1014.

J.V. Leonard, A.H. Schapira, Mitochondrial respiratory chain disorders II: neurodegenerative disorders and nuclear gene defects, Lancet 355 (2000) 389–394.

M. Patel, Mitochondrial dysfunction and oxidative stress: cause and consequence of age-related cognitive declines, Nat. Med. 37 (2004) 1951–1962.

G. Barone-Rochette, E. Vautrin, M. Rodiere, A. Broisat, G. Vanzetto, First magnetic resonance coronary artery imaging of bioreosorbable vascular scaffold in patient, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 229.

K. Schroder, J. Tschopp, The inflammasomes, Cell 140 (2010) 821–832.

T. Sutorow, J. Henao, D. Elinar, R. Flavell, Inflammamomes in health and disease, Nature 481 (2012) 278–286.

H. Li, S. Zhang, F. Li, L. Qin, Nlrp1 attenuates apoptosis and inflammatory responses in myocardial ischemia by inhibiting MAVS-dependent nlrp3 inflamma- somes and cardioprotective pathways are involved in diet-induced exacerbation of myocardial ischemia/reperfusion injury in mice, Oxid. Med. Cell. Longev. 2016 (2016) 3486037.

R. Mastrocola, C. Penna, F. Tullio, S. Fennie, D. Nigro, F. Chiazzia, V. Seraceo, F. Tullio, G. Allottasi, P. Pilapriro, M. Aragno, Maladaptative modulations of nlrp3 inflamma- somes and cardiprotective pathways are involved in diet-induced exacerbation of myocardial ischemia/reperfusion injury in mice, Oxid. Med. Cell. Longev. 2016 (2016) 5271251.

H.H. Szezo, S. Liu, Y. Soong, S.V. Sehan, L. Cohen-Gould, V. Manichev, L.C. Feldman, T. Guerriero, Angiogenin overexpression after acute ischemia prevents prolonged upregulation of il-1beta and il-18 and arrests cell k., J. Am. Soc. Nephrol. 28 (2017) 1437–1449.

J.M. Lee, G.J. Zipfel, D.W. Choi, The changing landscape of ischemic brain injury mechanisms, Nature 399 (1999) A7–A14.

M.A. Moskowitz, E.H. Lo, C. Iadecola, The potential role of mitochondrial dys- function in stroke-prone spontaneously hypertensive rats, Neurosci. Lett. 535 (2013) 104–109.

G. Barone-Rochette, E. Vautrin, M. Rodiere, A. Broisat, G. Vanzetto, First magnetic resonance coronary artery imaging of bioreosorbable vascular scaffold in patient, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 229.

K. Schroder, J. Tschopp, The inflammasomes, Cell 140 (2010) 821–832.

T. Sutorow, J. Henao, D. Elinar, R. Flavell, Inflammamomes in health and disease, Nature 481 (2012) 278–286.
control of neuronal survival by the p38-Akt signaling pathway. Curr. Opin. Neurobiol. 11 (2001) 297–305.

[109] C. Chen, L.C. Edelstein, C. Gelinas, The rel/nf-kappaB family directly activates expression of the apoptosis inhibitor bcl-xL. Mol. Cell. Biol. 20 (2000) 2607–2615.

[110] Z.L. Chu, T.A. McKinsey, L. Liu, J.J. Gentry, M.H. Malim, D.W. Ballard, Suppression of tumor necrosis factor-induced cell death by inhibitor of apoptosis c- iap2 is under NF-kappaB control. Proc. Natl. Acad. Sci. USA 94 (1997) 10052–10056.

[111] P.H. Chan, Mitochondria and neuronal death/survival signaling pathways in cerebral ischemia, Neurochem. Res. 29 (2004) 1943–1949.

[112] G. Deroua, A. Sabbekar, P. Maillot, The role of various peroxisome proliferator-activated receptors and their ligands in clinical practice. J. Cell. Physiol. 233 (2018) 153–161.

[113] G. Chimenti, J.C. Frucht, B. Staelens, Peroxisome proliferator-activated receptors 5–6 bind to nuclear receptors involved in lipid metabolism and inflammation. Inflamm. Res. 49 (2000) 497–505.

[114] Y.C. Chuang, T.K. Lin, H.Y. Huang, W.N. Chang, C.W. Liu, S.D. Chen, A.Y. Chang, S.H. Chan, Peroxisome proliferator-activated receptors gamma/mitochondrial uncoupling protein 2 signaling protects against severe induced neuronal cell death in the hippocampus following experimental status epilepticus, J. Neuroinflamm. 9 (2012) 184.

[115] Y.C. Chuang, T.K. Lin, D.Y. Yang, J.L. Wang, C.W. Liu, S.D. Chen, Peroxisome proliferator-activated receptor-gamma dependent pathway reduces the phosporylation of dynamin-related protein 1 and ameliorates hippocampal injury induced by global ischemia in rats, J. Biochem. Sci. 23 (2016) 44.

[116] P. Delerive, J.C. Frucht, B. Staelens, Peroxisome proliferator-activated receptors in inflammation control. Curr. Med. Chem. 16 (2009) 453–458.

[117] M. Ricote, A.C. Li, T.M. Willson, C.J. Kelly, C.K. Glass, The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation, Nature 391 (1998) 79–82.

[118] Y.W. Hong, H.D. Tai, V.S. Eberling, J.S. Wu, T.N. Lin, Anti-apoptotic actions of PPAR-gamma against ischemic stroke, Mol. Neurobiol. 41 (2010) 180–186.

[119] J.S. Wu, W.M. Chen, Y.S. Tsai, Y.T. Chen, W.H. Hong, H.D. Tai, Y.C. Chen, J.Y. Liou, S.K. Shyue, J.J. Chen, et al., Liganded-activated peroxisome proliferator-activated receptor-gamma protects against ischemic cerebral infarction and neuronal apoptosis by 14-3-3 epsilon upregulation, Circulation 119 (2009) 1124–1134.

[120] J. Gambou, D.A. Blankenship, J.P. Niemi, G.E. Landreth, M. Karl, E. Hilow, S. Kondarajuar, Extension of the neuroprotective time window for thiol-disulphide dioxigenesis in ischemic stroke is dependent on time of reperfusion, Neuroscience 170 (2010) 846–857.

[121] A. Patzer, Y. Zhao, I. Stock, P. Gohike, T. Herdegen, J. Culman, Peroxisome proliferator-activated receptor-gamma (ppargamma) differently modulate the inter-leukin-6 expression in the peri-infarct cortical tissue in the acute and delayed phases of cerebral ischemia, Eur. J. Neurosci. 28 (2008) 1786–1794.

[122] Y. Zhao, A. Patzer, T. Herdegen, P. Gohike, J. Culman, Activation of cerebral peroxisome proliferator-activated receptor gamma promotes neuroprotection by attenuation of neuronal cytochrome-c2 expression after focal cerebral ischemia in rats, FASEB J. 20 (2006) 1162–1175.

[123] D. Shimizu, I. Inoue, M. Sawada, D. Furuya, H. Nagoya, J.H. Greenberg, A Peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not permanent ischemia, Stroke 36 (2005) 353–359.

[124] T.N. Kerman, C.M. Vissoci, K.L. Furie, L.H. Young, S.E. Inuzuchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, et al., Pioglitazone after ischemic stroke or transient ischemic attack, N. Engl. J. Med. 374 (2016) 1321–1331.

[125] M. Lee, J.J. Saver, H.W. Liao, C.H. Lin, B. Ovbiagele, Pioglitazone for secondary prevention of cerebral ischemic stroke: a systematic review and meta-analysis, Stroke 48 (2017) 388–393.

[126] P. PUigserver, Z. Wu, C.W. Park, R. Graves, M. Wright, B.M. Spiegelman, A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis, Cell 92 (1998) 829–839.

[127] B.N. Finck, D.P. Kelly, Pgc-1 coactivators: inducible regulators of energy metabolism, Trends Endocrinol. Metab. 12 (2001) 393–400.

[128] P. PUigserver, J. Rhee, J. Donovan, C.J. Walkey, J.C. Yoon, F. Oriente, D. Knutti, A. Kralli, Pgc-1, a versatile coactivator, Trends Endocrinol. Metab. 12 (2001) 393–400.

[129] J. Gamboa, D.A. Blankenship, J.P. Niemi, G.E. Landreth, M. Karl, E. Hilow, S. Kondarajuar, Extension of the neuroprotective time window for thiol-disulphide dioxigenesis in ischemic stroke is dependent on time of reperfusion, Neuroscience 170 (2010) 846–857.

[130] A. Patzer, Y. Zhao, I. Stock, P. Gohike, T. Herdegen, J. Culman, Peroxisome proliferator-activated receptor-gamma (ppargamma) differently modulate the inter-leukin-6 expression in the peri-infarct cortical tissue in the acute and delayed phases of cerebral ischemia, Eur. J. Neurosci. 28 (2008) 1786–1794.

[131] Y. Zhao, A. Patzer, T. Herdegen, P. Gohike, J. Culman, Activation of cerebral peroxisome proliferator-activated receptor gamma promotes neuroprotection by attenuation of neuronal cytochrome-c2 expression after focal cerebral ischemia in rats, FASEB J. 20 (2006) 1162–1175.

[132] D. Shimizu, I. Inoue, M. Sawada, D. Furuya, H. Nagoya, J.H. Greenberg, A Peroxisome proliferator-activated receptor-gamma agonist reduces infarct size in transient but not permanent ischemia, Stroke 36 (2005) 353–359.

[133] E.A. Schon, G. Manfredi, Neuronal degeneration and mitochondrial dysfunction, J. Neurochem. 77 (2001) 1794–1796.

[134] H.R. Zhu, Z.Y. Wang, X.L. Zhu, X.X. Wu, E.G. Li, Y. Xu, Icariin protects against middle cerebral artery occlusion in the adult rat, Neuropathol. Appl. Neurobiol. 29 (2003) 458–461.

[135] C. Chen, L.C. Edelstein, C. Gelinas, The rel/nf-kappaB family directly activates expression of the apoptosis inhibitor bcl-xL. Mol. Cell. Biol. 20 (2000) 2607–2615.

[136] Z.L. Chu, T.A. McKinsey, L. Liu, J.J. Gentry, M.H. Malim, D.W. Ballard, Suppression of tumor necrosis factor-induced cell death by inhibitor of apoptosis c- iap2 is under NF-kappaB control. Proc. Natl. Acad. Sci. USA 94 (1997) 10052–10056.

[137] P.H. Chan, Mitochondria and neuronal death/survival signaling pathways in cerebral ischemia, Neurochem. Res. 29 (2004) 1943–1949.

[138] G. Deroua, A. Sabbekar, P. Maillot, The role of various peroxisome proliferator-activated receptors and their ligands in clinical practice. J. Cell. Physiol. 233 (2018) 153–161.

[139] G. Chimenti, J.C. Frucht, B. Staelens, Peroxisome proliferator-activated receptors 5–6 bind to nuclear receptors involved in lipid metabolism and inflammation. Inflamm. Res. 49 (2000) 497–505.

[140] H.R. Zhu, Z.Y. Wang, X.L. Zhu, X.X. Wu, E.G. Li, Y. Xu, Icariin protects against brain injury by enhancing sirt1-dependent PGC-1α expression in hippocampus, Neuropharmacology 59 (2010) 70–76.
M. van Gurp, N. Festjens, G. van Loo, X. Seelens, P. Vandenabeele, Mitochondrial intermembrane proteins in cell death, Biochem. Biophys. Res. Commun. 304 (2003) 487–497.

X. Wang, The expanding role of mitochondria in apoptosis, Genes Dev. 15 (2001) 2922–2933.

A.R. Anzelt, R. Maizy, K. Przyklenk, T.H. Sanderson, Mitochondrial quality control and disease: Insights into ischemia-reperfusion injury, Mol. Neurobiol. (2017).

N. Maruzhina, Y. Ohsumi, T. Yoshimori, Autophagosome formation in mammalian cells, Cell Struct. Funct. 27 (2002) 421–429.

L.L. Hu, J.L. Wang, X.H. Wen, N. Yang, Y. Qian, Cultivation of aerobic granular sludge in sbr by seeding anaerobic granular sludge, Huan Jing Ke Xue 25 (2004) 74–77.

J. Kopitz, G.O. Kisen, P.B. Gordon, P. Bohley, P.O. Seglen, Nonselective autophagy of cytosolic enzymes by isolated rat hepatocytes, J. Cell Biol. 111 (1990) 941–953.

A. Khaminets, C. Behl, I. Dikic, Ubiquitin-dependent and independent signals in selective autophagy, Trends Cell Biol. 26 (2016) 6–16.

C. Kraft, F. Reggiori, M. Peter, Selective types of autophagy in yeast, Biochim. Biophys. Acta 1793 (2009) 1404–1412.

V. Rogov, V. Dotech, T. Johansen, V. Kirkin, Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy, Mol. Cell 53 (2014) 167–178.

B.P. Meloni, A.J. Meade, D. Kiti孔molusk, N.W. Knuecky, Characterisation of neuronal cell death in acute and delayed in vitro ischemia (oxygen-glucose deprivation) models, J. Neurosci. Methods 195 (2011) 67–74.

F. Tian, K. Deguchi, T. Yamashita, Y. Ohta, N. Morimoto, J. Shang, X. Zhang, N. Liu, Y. Ibeda, T. Matsuura, et al., In vivo imaging of autophagy in a mouse stroke model, Autophagy 6 (2010) 1107–1114.

S. Carloni, S. Girelli, C. Scopa, G. Buonocore, M. Longini, W. Balduini, Activation of autophagy and Akt/CREB signaling play an equivalent role in the neuroprotective effect of rapamycin in neonatal hypoxia-ischemia, Autophagy 6 (2010) 366–377.

M. Coike, M. Shibata, M. Tadakoshi, K. Gotot, M. Komatsu, S. Wagsri, N. Kawahara, K. Kuida, S. Nagata, E. Kominami, et al., Inhibition of autophagy prevents hippocampal pyramidal neuron death after hypoxic-ischemic injury, Am. J. Pathol. 172 (2008) 454–469.

F. Mouton-Liger, M. Jacoupy, J.C. Corvol, O. Corti, Pink1/parkin-dependent mitophagy, Mol. Cell 53 (2014) 167–178.

R.F. Roberts, M.Y. Tang, E.A. Fon, T.M. Durcan, Defending the mitochondria: the F. Mouton-Liger, M. Jacoupy, J.C. Corvol, O. Corti, Pink1/parkin-dependent mitophagy and mitochondrial-derived vesicles, Int. J. Biochem. Cell Biol. 79 (2016) 427–436.

G. Ashrafi, T.L. Schwarz, The pathways of mitophagy for quality control and elimination of mitochondria, Cell Death Differ. 20 (2013) 31–42.

T.G. McWilliams, M.M. Muqit, Pink1 and parkin: emerging themes in mitochon-}

J.W. Yu, M.S. Lee, Mitochondria and the nlrp1 inflammasome: physiological and pathological relevance, Arch. Pharm. Res. 39 (2016) 1503–1518.

R. Zhou, A.S. Yardi, P. Mena, J. Tesch, A role for mitochondria in nlrp3 inflammasome activation, Nature 469 (2011) 221–225.

Q. Ma, S. Chen, Q. Hu, H. Feng, J.H. Zhang, J. Tang, Nlrp3 inflammasome contributes to inflammation after intracerebral hemorrhage, Ann. Neurol. 75 (2014) 209–219.

S.E. Lakhan, A. Kirchgesner, M. Hofer, Inflammatory mechanisms in ischemic stroke: therapeutic approaches, J. Transl. Med. 7 (2009) 97.

O.A. Harari, J.K. Liao, Nf-kappab and innate immunity in ischemic stroke, Ann. N. Y. Acad. Sci. 1207 (2010) 32–40.

D.Y. Fann, S.Y. Lee, S. Manzano, S.C. Tang, M. Gelderblom, P. Chunduri, C. Bernreuther, M. Glatzle, Y.L. Cheng, J. Thumdid, et al., Intravenous immunoglobulin suppresses nlrp1 and nlrp3 inflammasome-mediated neuronal death in ischemic stroke, Cell Death Dis. 4 (2013) e790.

L. Lammerding, A. Slowik, S. Johann, C. Beyer, A. Zendeled, Poststroke inflammasome expression and regulation in the peri-infarct area by genonid steroids after transient focal ischemia in the rat brain, Neuroendocrinology 103 (2016) 460–475.

F. Yang, Z. Wang, X. Wei, H. Han, X. Meng, Y. Zhang, W. Shi, F. Li, T. Xin, Q. Pang, et al., Nlrp3 deficiency ameliorates neurovascular damage in experimental ische-mic stroke, J. Cereb. Blood Flow Metab. 34 (2014) 660–667.

D.Y. Fann, Y.A. Lim, Y.L. Cheng, K.Z. Lok, P. Chunduri, S.H. Baik, G.R. Drummond, S.T. Dheen, C.G. Sohey, D.G. Jo, et al., Evidence that nsf-kappab and mapk signaling promotes nlrp1 inflammasome activation in neurons following ischemic stroke, Mol. Neurobiol. (2017).