The Role of Mitochondrial Biogenesis in Ischemic Stroke

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Abstract

Ischaemic stroke is a sudden neurological disorder caused by localised cerebral ischaemia and persistent cerebral infarction. Occlusion of large arteries due to atherothrombosis, cerebral embolism (i.e., embolic infarction), no thrombotic occlusion in small, deep cerebral arteries (i.e., lacunar infarction), and stenosis of proximal arteries due to hypotension leading to decreased cerebral blood flow in arterial supply zones are the most common causes of ischemic stroke (i.e., hemodynamic stroke). It is now known that organelles play an important role in various signaling events and cellular functions. The molecular mechanisms of mitochondria are involved in cerebral ischemia by generating and scavenging reactive oxygen species, apoptosis, biogenesis, mitochondrial dynamics, and inflammation are all examples of electron transport chain dysfunction. More knowledge about the involvement of mitochondria in ischemia-induced neuronal death and neuronal protection will contribute to the development of better treatment programs for stroke syndromes such as ischemic stroke.

Keywords: ischemic stroke; mitochondrial biogenesis; neuronal death; electron transport chain

1. Introduction

Stroke is the most common cause of mental and physical disability and has a high mortality rate in industrialized countries [1]. Rupture or occlusion of a blood vessel causes stroke. Stroke-related impairments always occur at onset (unlike brain tumor symptoms, which gradually worsen) and last longer than 24 hours. They are associated with visible cerebral vascular damage on neurological examination and imaging [2]. The pathophysiology of cerebral ischemic stroke consists of hypoxia and vascular damage, followed by inflammation, apoptosis, etc., resulting in neuronal damage and impaired brain function [3]. According to current guidelines, Intravenous thrombolysis (IVT) and tissue plasminogen activator (tPA) is the first choice of treatment for acute ischemic stroke [4]. Due to the limited time window of therapy, only about 8% of patients are eligible for tPA [5].

Mitochondria are multifunctional organelles involved in many metabolic activities, including energy production and synthesis of biomolecules [6–8]. Shape and distribution of mitochondria within the cell vary with time and reflect the metabolic state of a particular cell type [7]. They organize themselves into a tubular network within the cell that is constantly changing through cell division and fusion. The network breaks down into parts that spontaneously reassemble when mitochondria are removed from a cell [8,9]. Isolated mitochondria are capable of respiration and ATP production. They retain the composition, structure, and potential of their membranes, as well as their ability to fuse and import proteins from the environment [10,11]. Dynamic mitochondrial imbalance, free radical formation, calcium accumulation, intrinsic cell death activation, and finally cell death occurs due to negative stimuli as they do in neurodegenerative diseases [12,13].

Mitochondrial biogenesis is a property of mitochondria that generates new mitochondria from existing mitochondria [14]. Therefore, maintaining or improving mitochondrial activity may be a therapeutic strategy for neurodegenerative diseases. Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) co-activator-1alpha (PGC-1) regulates this biogenesis process. PGC-1 activates nuclear respiratory factors 1 and 2 (NRF1 and NRF2) and mitochondrial transcription factor A via phosphorylation or deacetylation (Tfam). When this PGC-1-NRF-Tfam pathway is activated, mitochondrial DNA, proteins and new mitochondria are synthesized [15]. There is evidence of a close association between neuronal cell death and excessive production of reactive oxygen species (ROS)
in some neurological diseases, including Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson’s disease (PD), ischemic stroke, epilepsy, and traumatic brain injury (TBI) [16,17]. Elevated ROS levels damage brain tissue structural and functional integrity, a process critical to the pathophysiology of cerebral ischemia [18–20].

The remarkable role of mitochondrial dysfunction and excessive oxidative stress in the ischemic cascade has been well established. Recent research has shown that mitochondrial biogenesis and ROS detoxification are two crucial endogenous protective mechanisms in acute cerebral ischemia and chronic neurodegenerative diseases [20–22]. Therefore, preventing the adverse effects of oxidative stress and improving mitochondrial function may be promising strategies for treating ROS-related diseases, including ischemic stroke.

2. Pathophysiology of Ischemic Stroke

According to the National Institute on Aging, stroke is the leading cause of mortality and morbidity in individuals aged >65 [23]. There are two types of strokes: hemorrhagic and ischemic, with ischemic strokes being the most common. Hemorrhagic strokes occur when a blood vessel ruptures and bleeds into the brain, while ischemic strokes occur when a blood clot blocks or severely narrows an artery that supplies blood to the brain. Ischemic stroke causes irreversible damage in the core of the brain, surrounded by reversible damage in the penumbra. The extent of damage varies depending on how long blood flow was obstructed. The longer the reperfusion process takes, the greater the injury [24]. Ischaemia occurs mainly in the infarct core and ischaemic penumbra. Within minutes, blood flow in the infarct core falls below the threshold of energy failure (i.e., 15%–20%), resulting in permanent damage to the infarct core, which may never recover [25]. Functions within the ischaemic penumbra may be impaired, although structural integrity is maintained. The cells in the penumbra can be rescued by vigorous reperfusion, and there is adequate collateral circulation to meet the glucose and oxygen needs of the neurons [24,26].

After stroke, reperfusion occurs in various tissues including the brain, heart, and kidneys. After reperfusion, further damage may occur due to increased Ca^{2+} and ROS levels in the tissues. Tissue damage caused by reperfusion is essentially a molecular and cellular process [27]. Excessive ROS production impairs cellular antioxidant defense mechanisms, leading to decreased free radical scavenging and eventual cell death. Reperfusion-induced ROS damage damages DNA, proteins, and lipids and impairs mitochondrial function [28]. After reperfusion injury, impaired mitochondrial function leads to decreased activity and ATP concentrations. Reperfusion-induced oxidative stress is also associated with mitochondrial DNA damage. ROS can damage cells or induce cell death via necrosis or apoptosis (Fig. 1) [29]. Accumulation of reactive oxygen species and calcium ions increases membrane permeability and leads to cell death. Despite their low energy stores, neurons have higher energy requirements than other brain cells. Mitochondrial failure develops minutes after ischemia due to glucose and oxygen deficiency, resulting in decreased ATP synthesis and excess ROS. ATP deficiency is a significant trigger for ischemic cascades, including failure of membrane ion pumps; cellular potassium efflux; sodium, chloride, and water influx; and membrane depolarization [30–32].

Many processes are associated with neuronal loss and cell death after stroke, including mitochondrial dysfunction, excitotoxic cell damage, free radical production, protein misfolding, acid toxicity, and inflammation [33,34].

Regulated cell death, such as apoptosis, autophagy, pyroptosis, and necroptosis, is induced by ischemia and contributes to brain damage after stroke. The cell death mechanisms may regulate each other to some extent [35,36]. Mitochondria are an essential regulator of stress signals [37]. Ischemia impairs mitochondrial respiratory activity and membrane potential, triggering a cascade that ultimately leads to neuronal death (Fig. 2) [38]. Depolarized mitochondria produce an excess of ROS due to their depolarization. The accumulation of ROS and calcium causes the membrane permeability transition to open. This releases cytochrome c, which activates effector caspases and eventually terminates apoptosis [39]. Disruption of signaling pathways may gradually interrupt or delay malignant responses and eventually lead to cell death. Therefore, you should understand mitochondrial biogenesis.

3. Structure and Function of Mitochondria

Double-membraned intracellular organelles such as mitochondria are found in all cells and are widely distributed. The outer membrane of the phospholipid bilayer contains protein channel structures that allow molecules with a maximum molecular weight of 10 kDa to pass through, including water, ions, nutrient molecules, ADP, and ATP. The inner membrane layer acts as a reactive apparatus for energy metabolism in the mitochondria. It contains electron transport protein complexes, ATP synthesis complexes, and ATP/ADP transport proteins. Water, oxygen, and carbon dioxide can pass through the inner membrane. The mitochondrial ETC (electron transport chain) plays an essential role in cellular energy production because it most strongly influences the process of oxidative phosphorylation, which involves several enzyme complexes (i.e., complexes I to V) in the inner mitochondrial membrane [40,41]. As biochemically demonstrated, the central part of ATP is used for neuronal electrical activity [42]. For neurons to survive and be excitable, mitochondria must provide sufficient energy. In addition to energy production, mitochondria are an important source of ROS and regulate apoptosis and neurodegenerative diseases [43–45].
Fig. 1. There are several factors that lead to mitochondrial dysfunction, including mitochondrial fission and fusion, mitochondrial-induced apoptosis, and mitochondrial phagocytosis. Oxidative stress caused by cerebral ischemia activates mitochondrial death signals, ASK1 activates JNK via MKK4. Activated JNK disrupts the balance of Bcl-2 proteins and mitochondrial membranes, leading to DNA damage and eventually neuronal death. In addition, mitochondrial cytochrome c can induce apoptosis and lead to neuronal cell death. Injury to neurons leads to ischemia, hypoxia, acidosis, and abnormal concentrations of ions, such as calcium and iron. Apaf-1, apoptosis-activating factor-1; ASK1, apoptosis signal-regulating kinase 1; cyt c, cytochrome c; FasL, Fas ligand; JNK, c-Jun–terminal kinase; NAD, nicotinamide adenine dinucleotide; PARP, poly (ADP-ribose) polymerase; ROS, reactive oxygen species; AIF, Apoptosis-inducing factor.
Mitochondria have been thought to spend their entire lives inside cells. Recently, there is evidence of intercellular exchange between healthy and injured cells by mitochondrial transfer. Recipient cells can take up and reprogram the released mitochondria to activate cell survival signals.

Mitochondria are highly active organelles that divide purposefully, fuse, and migrate through axons and dendrites [53]. Mitochondria in neurons arise from a highly dynamic compartment in form and function, including the movement of mitochondria through neuronal segments and the strategic placement of mitochondria at sites where ATP supply and calcium handling are required. And ions and substrates mediate a highly regulated link between neuronal activity and mitochondrial function. Mitochondria are critical for neuron survival, neurotransmission, and plasticity [54,55]. Neurons are increasingly dependent on mitochondrial activity to establish membrane excitability and to carry out complex neurotransmission and plasticity processes [56]. Mitochondrial dynamics and metabolic changes in human neurogenesis were studied using neural progenitor cell (NPCs) generated from human pluripotent stem cells [57,58].

At different stages of neuronal development, the expression patterns of metabolic genes were studied. As NPCs differentiate, the expression of mitofusin 2 (MFN2), an important component of mitochondrial fusion, increases [57]. MFN2 deficiency inhibits neuron formation in NPCs, whereas overexpression promotes neuronal development, suggesting a crucial function of mitochondrial dynamics in human neurogenesis. During differentiation of NPCs into neurons, expression of the essential glycolytic genes Hexokinase 2 (HK2) and Lactate Dehydrogenase A (LDHA) is reduced. However, transcript levels of most oxidative phosphorylation (OXPHOS) genes remain constant, as during neurogenesis in the adult hippocampus [58]. Mitochondria are concentrated in the pre- and post-synapses of the formed neurons, where there is a substantial energy demand [59,60]. At synaptic terminals, mitochondria supply local ATP to neurons and regulate cytosolic calcium levels. Neuron function would be impaired if mitochondria could not communicate with the center throughout development and beyond [61]. Astrocytes are essential components of the central nervous system as they are involved in neurodevelopment, neurotransmission, cerebral metabolism, and control of blood flow [62]. Normal astrocytes protect neurons from oxidative stress and excitotoxicity [63,64]. Dysfunctional astrocytes can produce harmful substances that cause neuronal damage [65]. Although mitochondria are derived from internal nuclei for energy production and survival, they can also be released into the extracellular environment [66]. The ability of neuroglia to maintain these protective mechanisms may depend on the integrity of their mitochondria, as inhibition of astrocytic mitochondria provides a source of energy to neurons threatened with cell death [65]. Examples include retinal neurons that transport mitochondria to astrocytes for recycling and disposal and bone marrow-derived stromal cells that transport mitochondria to alveoli to protect them from acute lung injury [67,68]. Recently, it was hypothesized that neurons dis-
charge damaged mitochondria and recycle them into astro-
cytes [67]. Because of this ability to exchange mitochon-
dria, it is conceivable that cells in the CNS communicate
with each other.

Additionally, astrocytes can provide functional mito-
chondria for neurons. A calcium-dependent mechanism
involving the cluster of differentiation 38 (CD38)/cyclic
ADP-ribose signaling pathway regulates the ability of an
astrocyte to release extracellular mitochondrial particles.
In mice, transient local cerebral ischaemia causes astro-
cytic mitochondria to invade neighbouring neurones and
enhances cell survival signals. Simultaneous suppression
of CD38 signaling decreased extracellular mitochondrial
transfer and worsened neurological status [48]. Astrocytes,
another subset of glial cells in the brain, perform impor-
tant physiological roles, including neuroprotective effects
in the A2 state and neuroinflammatory functions in the A1
state. In animal models, active microglia rapidly gener-
ate the A1 state of astrocytes after brain injury, leading to
further neuronal damage and cell death [69]. Drp1/Fis1-
triggered enhanced fission of mitochondria in activated mi-
croglia results in the production of fragmented and damaged
mitochondria that are rejected by these cells. Defective ex-
tracellular mitochondria, therefore, contribute to the prop-
agation of neurodegenerative signals from microglia [70].
This study shows that extracellularly damaged mitochon-
dria release more damaged mitochondria from microglia
when they lose their immune-privileged state and that dam-
age extracellular mitochondria play a direct role in disease
propagation by acting as effectors of the innate immune re-
sponse on nearby astrocytes and neurons. Fragmented mi-
 tochondria have been detected in clinical and experimenta-
 l studies of biofluids from individuals with subarachnoid
hemorrhage and stroke [48,71]. While extracellularly in-
jured mitochondria are harmful, the mitochondrial transfer
is beneficial, as demonstrated in a mouse model of acute
lung injury and a stroke model [48,68]. Joshi et al. [70]
show that the ratio of damaged to functional mitochondria
in the extracellular environment, determined by the extent
of pathological fission in donor microglia, affects the fate
of neurons.

5. Mitochondrial Biogenesis in
Neurodegeneration

The gradual loss of neurones and tissue damage in the
brain is known as neurodegeneration. Because of their high
energy requirements, neurones are susceptible to damage
and death from dysfunctional mitochondria. Severe dam-
age to mitochondria leads to cell death because cells can
no longer generate sufficient energy. Many clinical and
physiological studies suggest that mitochondrial dysfunc-
tion and dynamics play a critical role in the development of
neurodegenerative diseases [72]. Mitochondrial biogenesis
is required to maintain mitochondrial homeostasis through-
out the mitochondrial life cycle to meet the physiological
needs of eukaryotic cells [73].

After long-term local cerebral ischemia, progressive
loss of mitochondrial DNA (mtDNA) suggests mitochon-
drial regeneration. Several studies have shown that creat-
ing a dense population of functional mitochondria reduces
ROS production [74]. Mitochondrial biogenesis is a pre-
cise process that requires both mitochondrial and nuclear
genomes. It often occurs in healthy cells that are constantly
dividing and fusing, whereas division (fission) after brain
trauma leads to fragmentation of the mitochondrial network
[75]. Increased biogenesis is associated with increased mi-
 tochondrial DNA copy number and increased mitochondrial
gene expression. Peroxisome proliferator-activated
receptor co-activator 1 alpha (PGC-1a), mitochondrial tran-
scription factor A (TFAM), nuclear respiratory factors 1 and
2 (NRF1 and NRF2), and mitochondrial transcription factor
B1 (TFB1M) are involved in mitochondrial biogenesis [76].
Several processes appear to be involved in the mitochon-
drial formation, including (1) outer and inner membrane
synthesis, (2) mitochondrial protein synthesis, (3) synthesis
and import of proteins encoded by the nuclear genome, (4)
lipid import, (5) mitochondrial DNA replication, (6) mito-
ochondrial Fusion and fission, and mitochondrial Fusion and
fission [77–80].

Due to altered physiological circumstances, such as
increased ATP consumption, the cell’s ability to produce
ATP is impaired. Cell division and repair, embryonic de-
velopment, changes in physiological state (e.g., sympathetic
stimulation, caloric restriction, exercise, cold stress, and en-
ergy deficiency), hormones (thyroid hormone, leptin, and
erythropoietin), and mitochondrial disease/damage (e.g.,
inflammation and hypoxia/ischemia) are all major triggers
of mitochondrial biogenesis [80]. Another important trig-
ger of mitochondrial biogenesis is mitochondrial oxidative
dysfunction, which contributes to various neurological dis-
orders, as shown by numerous studies [80].

It is emphasized that decreased mitochondrial biogen-
esis can lead to mitochondrial dysfunction, which is nec-
 essary for the development of neurodegenerative diseases.
These diseases have been linked to genes that produce pro-
teins associated with mitochondrial biogenesis [81].

AD is a common neurodegenerative disease charac-
terized by memory loss and cognitive impairment and man-
ifested by various neurological, mental, and behavioral
symptoms [82,83]. Recent studies have shown that mito-
ochondrial dysfunction is an essential and early feature
of AD, with reduced energy metabolism being one of the
most visible critical abnormalities of the disease [84]. Mi-
 tochondrial intervention may help slow the progression of
amyloid plaque (Aβ)-induced degradation and dysfunction.
These findings are supported by in vivo observations of mi-
 tochondrial accumulation in AD patients [85,86]. Dega-
dration of β-secretase controlled by PGC-1α, a transcrip-
tional co-activator, has been shown to control the forma-
tion of A (BACE1). PGC-1α is a transcription factor that
affects energy metabolism by regulating mitochondrial ac-
mitochondrial dysfunction in various tissues. Amyloid precursor protein (APP) is altered in the brains of patients with AD, with increased a-secretase activity contributing to pathological Aβ formation [87]. PGC-1 expression is reduced in the brains of patients with AD, and this has been linked to the pathological formation by altering the processing of APP through increased a-secretase activity.

Further studies have linked the expression of genes encoding proteins involved in mitochondrial biogenesis, such as PGC-1α, NRF1, NRF2, and TFAM, to the development of neurodegenerative diseases such as AD [74]. Significant downregulation of these genes is observed in AD and hippocampal cells and tissues, indicating a decrease in mitochondrial biogenesis [74]. However, due to the pleiotropic nature of PGC-1α, it is unclear how AD affects mitochondrial biogenesis signaling and whether these changes lead to mitochondrial dysfunction [74]. Parkinson’s disease (PD) is a degenerative neurological movement disorder of unknown etiology influenced by hereditary and environmental factors [88]. In the early and late stages of Parkinson’s disease (PD), significant reductions in putamen ATP and phosphocreatine levels and midbrain ATP levels as high-energy metabolites indicate mitochondrial dysfunction in mesostriatal dopaminergic neurons [89]. Genome-wide analysis of normal subjects and patients with PD revealed that PGC-1α, a key regulator of mitochondrial biogenesis, was reduced in patients with PD [90], suggesting that mitochondrial dysfunction plays a critical role in the cause of PD [91] has found evidence that the deficiency in PD is at or above the level of PGC-1α expression, which controls mitochondrial complex I function. Recent research has linked several proteins involved in familial PD, including α-syn, Parkin, PTEN-induced putative kinase 1 (PINK1), protein deglycase DJ-1 (Parkinson protein 7), and Leucine-Rich repeat kinase 2 (LRRK2 or Dardarin), to quality control and regulation of mitochondrial dynamics [92,93]. Amyotrophic lateral sclerosis (ALS) is a neurological disorder that manifests as gradual paralysis in adults and is a genetic disorder. In humans, the disease is associated with degeneration of motor neurons and selective loss in the spinal cord and brain, resulting in denervation of muscles and muscle wasting after denervation [94]. Postmortem spinal cord specimens from individuals with Lou Gehrig disease (ALS) show morphological and biochemical mitochondrial abnormalities, including decreased mitochondrial DNA copy number and decreased respiratory chain activity [95]. Mutations/deletions in mitochondrial genes have been associated with specific muscle and neuronal diseases [96]. Mitochondrial dysfunction can lead to certain damage to muscles or neurons.

PGC-1α is thought to have beneficial effects on muscles, including increased mitochondrial activity and muscle hypertrophy. Mitochondrial activity and biogenesis are preserved in late-stage disease, as is muscle function, delayed muscle wasting, and improved muscle tolerance. Although lifespan could not be extended, drugs that increase PGC-1α activity in muscles are beneficial for preserving muscle functionality throughout ALS [97]. Activation of peroxisome proliferator-activated receptors (PPARs) that interact with PGC-1α and control mitochondrial biogenesis in combination with this transcriptional co-activator is another strategy to increase PGC-1α signaling and improve mitochondrial function [98]. Another study conducted in cell cultures showed that Sirtuin 3 (SIRT3) protects against mitochondrial fragmentation and neuronal cell death during developing AD [99]. The regulating PPARα transcriptional activity in the central nervous system represents a novel approach to slowing ALS progression [100]. Mitochondria, important intracellular organelles that control cell life and death, are being investigated as potential therapeutic targets in pharmaceutical research.

6. The Role of Mitochondria in Ischemic Stroke

Mitochondria are critical for cell survival and death. Pathophysiological abnormalities transform mitochondria from essential organelles into activators of cell death [101,102]. Mitochondria play a crucial role in cell death by ischemia by impairing ATP synthesis and participating in apoptotic and necrotic pathways [103]. The main goal of stroke research is to elucidate the process of neuronal ischemic injury to improve functional outcomes. Neurons are more susceptible to ischemic damage than other cells because they are constantly dependent on an external energy supply. As excitable cells, neurons express many receptors for excitatory transmitters, especially at synapses [104]. In stroke, oxygen and glucose deprivation are the main components of tissue damage. OGD (oxygen-glucose deprivation) models are the most commonly used stroke in vitro models. Hydrogen peroxidase exposure or glutamate-induced excitotoxicity is another in vitro stroke model. Studies on brain slices or cultured neurons have contributed significantly to our knowledge of neuroprotective and ischemic injury processes [105]. Mitochondria produce energy and are very numerous in brain cells because neurons need a lot of ATP to function properly [106].

Mitochondria use an electron transport chain (ETC) to convert electron donor molecules such as reduced (NADH) nicotinamide adenine dinucleotide into energy through various oxidation/reduction processes. The compounds discussed here transfer electrons and support transmembrane proton transport, creating an electrochemical gradient that favors mitochondrial ATP synthesis [107]. Five enzyme complexes consisting of integral internal membrane proteins are found in ETC: NADH-CoQ reductase, Coenzyme Q (CoQ) cytochrome c reductase, succinate CoQ reductase, cytochrome c oxidase, and ATP synthase (complexes I–V) [108]. Cytochrome c and ubiquinone (CoQ) 1+ are two molecules that circulate freely in the complexes and control electron transport. Oxygen is the final electron acceptor.
Table 1. Some recent studies that by increasing biogenesis and improving mitochondrial function, protect against brain injuries caused by cerebral ischemia.

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</tr>
</tbody>
</table>

OGD/R, oxygen and glucose deprivation and reperfusion; PNGL, Notoginseng leaf triterpenes; MCAO, Middle cerebral artery occlusion; I/R, ischemia-reperfusion; NSCs, neural stem cells; OGD, oxygen glucose deprivation; AC, amlodipine camsylate; ETBR, endothelin B receptors; HPPNCs hippocampal neuronal cells; CTRP3, C1q/tumor necrosis factor-related protein-3; Drp1, dynamin-related protein 1; PP2A, protein phosphatase 2A; Ref, Reference.
in the inner mitochondrial membrane and generates an electrochemical proton gradient (IMM) [109]. ROS are mainly generated in this ETC, especially after reperfusion. Numerous findings suggest that most ROS generated during reperfusion is due to mitochondrial ETC, which exacerbates ischemic cell death [110]. After ischemia, the significant lack of ATP generation and the elevated levels of ROS trigger the mitochondrial death pathway by apoptosis [111]. After ischemia, brain cells produce less ATP, compromising membrane-bound channels required for normal cell function. Mitochondria generate significant ROS.

The superoxide anion radical is a precursor of several other potentially dangerous ROS, including hydroxyl, hydrogen peroxide, and peroxynitrite. Mitochondrial dysfunction is caused by oxidative stress, energy deficiency, and impaired calcium homeostasis in the cell. Reperfusion increases the production of ROS in mitochondria, and Ca^{2+} activates caspase-independent and caspase-dependent death pathways [112].

Mitochondria, as receptors for a variety of stimuli, trigger both caspase-independent (AIF, Apoptosis-inducing factor) and caspase-dependent (cytochrome c) cell death [113]. Ischemia promotes these processes and leads to necrotic and apoptotic death of brain cells. Inflammation is another critical factor in the pathophysiology of cerebral ischemia. Glial cell activation, infiltration by peripheral leukocytes, and damage-associated chemicals such as high mobility group protein 1, nucleotides, nucleic acid fragments, and purines trigger the inflammatory response after ischemia [114,115]. Acute systemic inflammatory stimuli increase the outcome of ischemic stroke, with the pro-inflammatory cytokine IL-1 playing a crucial role [116]. Recent research has shown that mitochondria alter their function in controlling the inflammatory response [117–119]. Mitochondria are the primary regulators of Neutrophil-Lymphocyte Ratio (NLR) Family Pyrin-Domain-Containing Protein 3 (NLRP3) inflammasome activation [120]: the outer mitochondrial membrane serves as an assembly platform for the inflammasome. It also induces pyroptosis and innate immune defense through caspase-1 and various pro-inflammatory cytokines [121,122]. Recent studies indicate that the NLRP3 inflammasome contributes to renal and cardiac ischemia [123–126]. This review focuses on the rapidly evolving and complex function of mitochondria in ischemic cerebral stroke. Understanding the fundamental processes behind the potentially protective activities of mitochondria may offer insights into developing new treatments.

7. Mitochondrial Biogenesis in Ischemic Stroke

The function of mitochondrial biogenesis in neurons is poorly understood. First, researchers investigated the transcriptional control of mitochondrial biogenesis in mice lacking the mitochondrial transcription factor peroxisome proliferator-activated receptor co-activator (PGC) 1. A ROS-mediated mechanism is involved in the progression of oxidative stress-induced neurodegeneration [127]. Hypoxia preconditioning increases PGC-1 expression in response to neuronal nitric oxide synthase (nNOS) activity. Oxidative stress is associated with widespread mitochondrial fission and neuronal death throughout the body. It has been shown that mitofusin 2, a mitochondrial Fusion protein, overexpression can reverse neuronal death [81]. For neuronal survival to occur, precise regulation of Fusion and fission must be maintained. Recent studies have also shown that hypoxia-ischemia stimulates mitochondrial production. Under hypoxia, mitochondrial DNA increases, as does the number of mitochondrial cells [128]. Hypoxia also increases the production of PGC-1, downstream mitochondrial transcription factors (mitochondrial transcription factor A and nuclear respiratory factor 1), and the mitochondrial protein heat shock protein 60 (HSP60). This breakthrough finding suggests that mitochondrial biogenesis is a novel endogenous neuroprotective response that can be activated.

Mitochondria are damaged after a fatal ischemic insult, and autophagy is triggered to remove damaged organelles from the cell. The maintenance of energy balance and calcium and zinc homeostasis is essential for neuronal function. Microsomal biogenesis is a crucial endogenous neuroprotective process that produces new functional mitochondria when the body is exposed to high-stress levels. A novel strategy for neuroprotection is to increase or accelerate mitochondrial biogenesis, a process unknown. Further studies are needed to understand the molecular basis of mitochondrial biogenesis after stroke. Other studies on the role of mitochondrial turnover, mitochondrial Fusion and fission mechanisms, and alternative transcriptional pathways after ischemia are warranted [129]. Identifying critical mediators of autophagy and mitochondrial biogenesis will lead to the identification of new therapeutic targets to enhance the beneficial effects of mitochondrial maintenance (Table 1, Ref. [3,130–136]).

8. Conclusions

The lack of ATP and nutrients in ischemia impairs the leading role of mitochondria in stroke pathology. The rapid degeneration of penumbral neurovascular units essentially requires a new effective therapeutic strategy for stroke. Recent evidence of mitochondrial transfer through the formation of TNT, cell Fusion or extracellular vesicles (EVs) and the potential restoration of mitochondrial function in promoting cell survival in numerous preclinical studies argues for stem cell-mediated mitochondrial transfer therapies in stroke. Mitochondria are mainly in the presynaptic nerve terminals of neurons. When ischemia occurs, neurons are likely to shift mitochondria for both disposal and recycling to respond quickly to the lack of energy caused by the condition. After ischemia, mitochondria cannot be re-
plenished promptly therefore because they must be transported long distances. Therefore, extracellular mitochondrial translocation may provide a new opportunity for neuroprotective strategies. Further research is needed to understand better the impact of mitochondrial biogenesis and function on ischemic stroke.

Author Contributions
BS, CBA, MN, and AN developed the concept and designed the study. VK, GIS, FE, and JBHO did a systematic search and prepared the first draft. All authors participated in the revising of the manuscript before submission. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate
Not applicable.

Acknowledgment
Not applicable.

Funding
This research received no external funding.

Conflict of Interest
The authors declare no conflict of interest.

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IMR Press


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