Redox Biology 16 (2018) 263–275

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Review article

Diverse roles of mitochondria in ischemic stroke

Jenq-Lin Yang[a], Sujira Mukda[a,b], Shang-Der Chen[a,c,d,*]

[a] Institute for Translation Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, 123 Dapi Road, Kaohsiung 83301, Taiwan, ROC
[b] Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, 25/25 Phuttamonthon 4 Road, Salaya, Nakhon Pathom 73170, Thailand
[c] Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, 123 Dapi Road, Kaohsiung 83301, Taiwan, ROC
[d] College of Medicine, Chang Gung University, 259 Wenhua 1st Road, Taoyuan 33302, Taiwan, ROC

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 an often overlooked target for the clinical treatment of stroke. Early studies of mitochondria focused on their bioenergetic role; however, these organelles are now known to be important in a wide range of cellular functions and signaling events. This review aims to summarize the current knowledge on the mitochondrial molecular mechanisms underlying cerebral ischemia and involved in reactive oxygen species generation and scavenging, electron transport chain dysfunction, apoptosis, mitochondrial dynamics and biogenesis, and inflammation. A better understanding of the roles of mitochondria in ischemia-related neuronal death and protection may provide a rationale for the development of innovative therapeutic regimens for ischemic stroke and other stroke syndromes.

1. Introduction

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

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

* Corresponding author at: Department of Neurology and Institute for Translation Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, 123 Dapi Road, Kaohsiung 83301, Taiwan.
E-mail address: chensd@adm.cgmh.org.tw (S.-D. Chen).

https://doi.org/10.1016/j.redox.2018.03.002
Received 22 January 2018; Received in revised form 1 March 2018; Accepted 6 March 2018
Available online 09 March 2018

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

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

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

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

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

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

2. Cerebral ischemic cascade involves mitochondrial function and ROS

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

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