Mitochondrial Dysfunction Involved in the Pathogenesis of ALS

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Contributor: Sayuri Yoshikawa , Kurumi Taniguchi , Haruka Sawamura , Yuka Ikeda , Ai Tsuji , Satoru Matsuda

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease, the pathogenesis of which is based on alternations in the mitochondria of motor neurons, causing their progressive death. A growing body of evidence shows that more efficient mitophagy could prevent and/or treat this disorder by suppressing mitochondrial dysfunction-induced oxidative stress and inflammation. Mitophagy has been considered one of the main mechanisms responsible for mitochondrial quality control.

ALS mitophagy ROS AMPK mTOR

1. Introduction

Mitochondrial activity and the generation of reactive oxygen species (ROS) are important for cell proliferation, survival, and/or differentiation [1]. In addition, many diseases, such as cardiac failure, cancer, and age-related pathological conditions, have been related to altered mitochondrial function [2]. For example, the energy deficiency resulting from local hypoxia during an ischemic heart attack leads to mitochondrial dysfunction, which could have arrhythmogenic consequences and lead to sudden cardiac death [3]. The significance of mitochondria has been emphasized in a variety of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). ALS is an incorrigible neurodegenerative disease whose etiology is based on the progressive death of motor neurons [4]. At present, ALS has no effective therapy. A better understanding of the mitochondrial regulating pathways may raise several promising neuroprotection perspectives in the effective treatment of ALS. Furthermore, the development of new treatments would be useful not only for the mitochondrial disorders of ALS but also for the wide spectrum of age-related neurodegenerative diseases.

The mitochondrion is the main place for adenosine triphosphate (ATP) synthesis, fatty acid β-oxidation, and ROS production [5]. Mitochondrial function and ATP production are crucial for neuronal cell survival and excitability [6]. However, mitochondrial dysfunction leads to the overproduction of ROS and neuronal apoptosis, which is closely related to neurodegenerative diseases [6]. To slow down the progression of the pathology of ALS, the high oxidative stress and mitochondrial activity of neurons should at least be improved. Mitophagy, which is a specific kind of autophagy, can selectively degrade damaged mitochondria to reduce mitochondrial dysfunction and maintain mitochondrial function. Thus, mutations in the genes that encode factors essential for mitophagy may result in the impairment of this process, which can lead to neurodegenerative conditions such as ALS [7]. For example, hypoxia is a common factor in several disease conditions, such as inflammation, which can lead to a depletion of oxygen and, eventually, through the production of ROS, directly to an alteration of intracellular proteins, lipids, or DNA [8].

Therefore, the control of the mitochondrial ROS level is of key relevance for maintaining cellular homeostasis [9]. The conserved pathway of mitophagy is required to prevent and/or counteract the pathogenic actions that may lead to neurodegeneration.

2. Mitochondrial Dysfunction Involved in the Pathogenesis of ALS

Mitochondria are pretty vigorous organelles whose number and activity can be adjusted to the changes in cellular energy metabolism by regulating their biogenesis, fusion/fission events, and removing damaged ones [5]. The most common reasons for mitochondrial dysfunction are hypoxia and the overproduction of ROS. In particular, oxidative stress caused by numerous inflammations is related to the development of many neurological complications [10]. Excessive ROS also induce oxidative stress and apoptosis in cells [11]. Typically, in cells, ROS are generated in the mitochondrial respiratory chain. Accordingly, mitochondrial dysfunction could also lead to neuronal cell death and/or apoptosis [12], which is associated with neurological complications, including Alzheimer's disease, Parkinson's disease, and Huntington's disease [13]. These oxidative stresses that include oxygen radicals could be intercepted [14]. In various neurodegenerative diseases such as ALS, several defects in mitochondrial function leading to oxidative stresses have been identified in underlying relations [15]. Indeed, this emphasizes the importance of healthy mitochondria for the maintenance of healthy neuronal functions.

Under physiological conditions, ROS could work as regulators of the mechanism for maintaining cellular redox homeostasis [16]. During oxidative phosphorylation, mitochondria could produce a superoxide anion by-product, which may be further changed into ROS [17]. Mitochondrial ROS consist of superoxide, hydrogen peroxide, and hydroxyl, which can modify lipids, proteins, and DNA, resulting in mitochondrial dysfunction and/or neuronal cell death [18]. Accumulation of damaged mitochondria and the overproduction of ROS will strengthen each other, which may finally lead to severe mitochondrial dysfunction. Mitochondrial ROS are also regulators of a cellular redox environment linked to cellular metabolic balance [19]. Accordingly, hindering too much production of ROS is considered an effective way to prevent oxidative damage to cells, including the neuron [20]. It may be indispensable to explore the roles of mitochondrial ROS in ALS. Antioxidants are the first safety to clear ROS [21]. In addition, there are various systems to withstand ROS-induced oxidative stresses, based on superoxide dismutase, catalase, and/or glutathione peroxidases. Considering the crucial role of mitochondria in cellular homeostasis, monitoring the quality of mitochondria may be important for avoiding neurodegenerative diseases including ALS [22]. In fact, functional defects in and altered morphology of mitochondria have been found in the spinal motor neurons of ALS patients [23]. Likewise, mislocalization and aggregation of mitochondria have been detected in the motor neurons of ALS patients. These observations suggest that the dysfunction of mitochondria may be a regular feature of ALS [24]. Therefore, mitochondrial quality control in many forms of molecular and/or cellular levels should be performed to prevent neurodegenerative diseases, including ALS.

Mitophagy, a mitochondrial quality control mechanism, selectively removes dysfunctional mitochondria to preserve mitochondrial function and maintain cellular homeostasis. In this process, impaired mitochondria are trapped and surrounded by autophagic membranes and further delivered to lysosomes, where they are degraded. It is well-

known that the clearance mechanism of damaged mitochondria can be a potent therapeutic strategy in cases of increased oxidative stresses [25]. Some physiologic or chemical faults in mitochondria may trigger mitophagy by disrupting the mitochondrial inner membrane, possibly with the involvement of ROS. Mitophagy has been proven to be related to the development of various diseases, including ALS [26]. For example, treatment with progesterone can prolong the survival time in a mouse model of ALS, which might be associated with enhanced autophagy in the spinal cord [27]. On the contrary, autophagy induction could accelerate the progression of ALS, most likely through the excessive mitochondrial clearance in motor neurons [28]. The balance between synthesis and degradation of mitochondria may be essential for maintaining mitochondrial and/or cellular homeostasis, and the modulation of mitophagy represents a promising therapeutic intervention.

With a complex etiology and no current cure for ALS, broadening the understanding of disease pathology is required to progress with patient care [29]. In general, mitophagy selectively degrades damaged mitochondria to suppress damaged mitochondria-derived ROS that would damage healthy mitochondria and ultimately result in mitochondrial dysfunction. As a major mechanism of mitochondrial quality control, mitophagy could degrade dysfunctional mitochondria to maintain mitochondrial integrity and function. Therefore, activated and/or appropriate mitophagy would prevent ROS from triggering oxidative stresses and inflammatory responses. In particular, counteraction of the process of oxidative stresses may be promising for prolonging life with ALS [30]. Looking for natural compounds with mitophagic actions would provide new insights into the therapeutic intervention for mitochondrial dysfunction-related diseases, including ALS. However, the therapeutic potential of autophagy modulation has not been fully exploited.

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