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LETTER TO THE EDITOR

Mitochondrial-Based Therapeutic Strategies for Intracerebral Hemorrhage

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Intracerebral hemorrhage (ICH) is a stroke subtype that is associated with high mortality and disability rate. Mitochondria dysfunction plays a crucial role in secondary brain injury (SBI) after ICH, and mitochondria take an important part in improving neurological function after ICH. This short communication summarizes ICH-induced mitochondrial dysfunction and related mechanisms including oxidative stress, cell death, mitochondria dynamics imbalance, mitochondrial transfer blocked, and abnormal clearance of damaged mitochondria. Also, the mitochondrial protection as a potential therapeutic target for ICH-induced SBI has been emphasized, which will provide promising strategies for clinical treatment.

Mitochondria, as eukaryotic energy supply organelles, have a double membrane structure: outer membrane and inner membrane. Mitochondrial cristae, a special substructure derived from the invagination of mitochondrial inner membrane (MIM), are the site where aerobic respiration occurs. Crista formation increases the surface area of the MIM. The neck-like area where the crest meets the inner membrane is called crista junctions (CJs). In addition, the respiratory chain electron transport chain complex protein and ATP synthase are anchored on the mitochondrial crest, which generate ATP through oxidative phosphorylation and provide energy for normal metabolic activities of cells. Also, the integrity of mitochondrial crest structure participates in the fission, fusion, and transportation of mitochondria, especially affecting the distal axonal synapses enriched with mitochondria in neuronal cells, and the clearance of damaged mitochondria and the replacement of healthy mitochondria in dendrites [1]. Therefore, the integrity of mitochondrial crest structure plays an irreplaceable role in the important life activities of mitochondria. Mitochondrial contact sites and crista tissue system (MICOS) is a key determinant of mitochondrial membrane structure integrity. In our team, we found that Mic60, a central subunit of MICOS, can take part in maintain mitochondrial junction integrity and induce mitophagy to clear the damaged mitochondria after ICH [2]. The structure integrity and remodeling of mitochondrial crest after ICH have rarely been reported, which can be a novel approach for mitochondrial research.

As "power factories" in nerve cells, mitochondria control almost every aspect of cellular function, including generating ATP, regulating calcium homeostasis, and maintaining redox state. Therefore, the dysfunction of mitochondria could promote the occurrence and development of various cellular damage processes, which are inevitably involved in the pathological process of stroke, including ICH. During ICH, the mitochondria were involved in neuronal cell death, reactive oxygen species (ROS) generation, neuroinflammation, and blood–brain barrier (BBB) disruption [3]. Besides, the hematoma component release may cause brain damage by generating free radicals including ROS, which are the causes of SBI after ICH. Mitochondria are the main organelles of ROS generation, and also the main targets for ROS attacks. Aberrant accumulation of ROS could induce cell death and tissue damage after ICH. It is well known that mitochondria participate in cell apoptotic progress, and neuronal cell apoptosis would occur after ICH. Series apoptosis-related proteins are located on or associated with mitochondria. B-cell lymphoma (BCL-2) family on mitochondria could take action both on anti-apoptosis (Bcl-2, Bcl-xL, and Bcl-w) and trigger apoptosis (Bad, Bax, Bim, Bak, and so on). Also, collapse of mitochondrial membrane potential (MMP) could induce proapoptotic protein release such as AIF and cytochrome C (cyto C). It has been reported that melatonin could alleviate ICH-induced mitochondrial dysfunction and neuronal apoptosis [4].

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In addition, with high energy consumption and long-term survival, neurons have precise mitochondrial quality control, which take a significant part in protecting neurons against ICH injury. Mitochondria dynamics including mitochondrial fission and fusion is an important mechanism of mitochondrial quality control in neurons. The balance of mitochondrial fission and fusion plays an essential role in maintaining the normal morphology and function of mitochondria and neuronal cell stability. Once this balance is broken, excessive mitochondrial fission or fusion occurs, resulting in the energy metabolism dysfunction, MMP collapse, cyto C release, and neuronal cell death. Dynamin-related proteins (DRPs), especially Drp1, participate in regulating mitochondrial fission and fusion. Drp1 is a crucial executor of neuronal mitochondrial fission, and its function is regulated by phosphorylation. It has been well established that phosphorylation at serine 616 of Drp1 promotes mitochondrial fission by translocating to mitochondrial membrane, while phosphorylation at serine 637 inhibits the ability of Drp-1 to promote mitochondrial fission. Adiponectin peptide (ANP) has been reported to exhibit the inhibition effect on Drp1-mediated mitochondrial fission, which then contributes to improve SBI induced by ICH [5].

Moreover, mitochondria dynamic could promote the clearance of damaged mitochondria, and mitophagy plays a critical role in this progress. Mitophagy is a neuroprotective mechanism that maintains mitochondrial homeostasis and health by removing impaired mitochondria in cells. In neurological disease, damaged mitochondria are selectively cleared by mitophagy through PINK1-Parkin1 pathway. PINK1, located on mitochondria, can recruit Parkin1 to mitochondria and induce mitophagy, and Mic60 has been reported to be involved in this progress after ICH [2]. Whereas excessive mitophagy could induce neuronal cell death in some research. Although the exact function of mitophagy is controversial, further research is needed to explore its effect in ICH. Furthermore, intercellular mitochondrial transport has a key function in the protection of neuronal injury. New compelling studies have shown that mitochondrial transfer to the damaged cells can help revive cells energetic in the recipient cells after stroke [6]. In ICH, it has been reported that mitochondria-derived peptide humanin improves ICH-induced SBI through participating mitochondria transfer and microglia phenotype change [7].

Mitochondrial injury is a considerable factor for brain injury after ICH, which is the early event of ICH. And it has been reported that the structure and function of mitochondria in neuronal cells remain relatively normal in the early stage of ICH. With the progression of ICH, mitochondrial structure and function are damaged, leading to ROS accumulating, neuronal cell death, fission and fusion imbalance, mitophagy blocked, and transport impaired. Therefore, mitochondria are notable drug targets for ICH therapy, and further researches are needed to focus on mitochondria during ICH.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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