EXPERIMENTAL CELL RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

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Review Article

Regulation of mitochondrial transport in neurons

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ARTICLE INFORMATION

Article Chronology:
Received 31 December 2014
Accepted 12 January 2015

Keywords:
Mitochondrial transport
Mitochondrial docking
Mitophagy
Motile mitochondria
Stationary mitochondria
Kinesin motors
Dynein motors
Syntaphilin
Synaptic activity

ABSTRACT

Mitochondria are cellular power plants that supply ATP to power various biological activities essential for neuronal growth, survival, and function. Due to unique morphological features, neurons face exceptional challenges to maintain ATP and Ca^{2+} homeostasis. Neurons require specialized mechanisms distributing mitochondria to distal areas where energy and Ca^{2+} buffering are in high demand, such as synapses and axonal branches. These distal compartments also undergo development- and activity-dependent remodeling, thereby altering mitochondrial trafficking and distribution. Mitochondria move bi-directionally, pause briefly, and move again, frequently changing direction. In mature neurons, only one-third of axonal mitochondria are motile. Stationary mitochondria serve as local energy sources and buffer intracellular Ca^{2+}. The balance between motile and stationary mitochondria responds quickly to changes in axonal and synaptic physiology. Furthermore, neurons are postmitotic cells surviving for the lifetime of the organism; thus, mitochondria need to be removed when they become aged or dysfunction. Mitochondria also alter their motility under stress conditions or when their integrity is impaired. Therefore, regulation of mitochondrial transport is essential to meet altered metabolic requirements and to remove aged and damaged mitochondria or replenish healthy ones to distal terminals. Defects in mitochondrial transport and altered distribution are implicated in the pathogenesis of several major neurological disorders. Thus, research into the mechanisms regulating mitochondrial motility is an important emerging frontier in neurobiology. This short review provides an updated overview on motor-adaptor machineries that drive and regulate mitochondrial transport and docking receptors that anchor axonal mitochondria in response to the changes in synaptic activity, metabolic requirement, and altered mitochondrial integrity. The review focuses on microtubule (MT)-based mitochondrial trafficking and anchoring. Additional insight from different perspectives can be found in other in-depth reviews.

Contents

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http://dx.doi.org/10.1016/j.yexcr.2015.01.004
0014-4827/

Please cite this article as: M.-Y. Lin, Z.-H. Sheng, Regulation of mitochondrial transport in neurons, Exp Cell Res (2015), http://dx.doi.org/10.1016/j.yexcr.2015.01.004

Introduction

In the human brain, a resting cortical neuron consumes ~4.7 million ATP molecules per second to power various biological functions [74]. Mitochondria are cellular power plants that supply more than 90% of the cellular ATP to support neuronal survival and function, such as axonal growth and branching, generation of action potentials, and synaptic transmission. Mitochondria are also involved in short-term synaptic plasticity and maintain and regulate neurotransmission by buffering presynaptic Ca^{+2} [25,29,60]. Therefore, loss of mitochondria from axonal terminal impairs synaptic transmission likely due to insufficient ATP supply or reduced Ca^{+2}-buffering capacity [19,31,54].

Neurons are polarized cells with dendrites and a thin long axon that can extend up to 1 m in motor and sensory neurons. To maintain energy homeostasis throughout the neuron, specialized mechanisms are required to efficiently deliver mitochondria to distal areas where energy supply and Ca^{+2} buffering capacity are in high demand [47,52]. Long-range mitochondrial transport depends upon MT-based motors. The axonal MTs are uniformly polarized, while the dendritic MTs exhibit mixed polarity. The uniform MT polarity has made axons particularly useful for elucidating mechanisms regulating mitochondrial transport: kinesin-1 (KIF5) motors drive anterograde transport distally whereas dynein motors mediate retrograde movement toward the soma. Energy powering motors to drive their cargo transport is from ATP hydrolysis [23]. Mitochondrial respiration provides the main ATP source, thus powering their own motility [72]. Both in vitro and in vivo live imaging in different types of neurons consistently reveals a complex motility pattern of mitochondrial transport along axons: mitochondria display bi-directional transport, frequent pause and change in direction, or persistent docking in certain regions. Thus, the mean velocity of neuronal mitochondria is highly variable, ranging from 0.32 to 0.91 μm/s [32].

In mature neurons, about 20–30% of axonal mitochondria are motile [10,25]; while ~15% mitochondria either briefly pause or dock at synapses; and ~14% motile mitochondria dynamically pass through presynaptic terminals. Our recent study [56] demonstrates that an anchored mitochondrion within presynaptic terminals provides a stable and continuous ATP supply. Conversely, in the absence of a mitochondrion within a terminal, there is no stable on-site ATP supply. A motile axonal mitochondrion passing through those terminals temporally supplies ATP, thus changing synaptic energy levels and influencing various ATP-dependent synaptic activities. This study revealed, for the first time, that the fast movement of axonal mitochondria is one of the primary mechanisms underlying the presynaptic variation. This provides new insight into the fundamental properties of the central nervous system to ensure the plasticity and reliability of synaptic transmission.

Axons and synapses are highly plastic and undergo spontaneous and activity-dependent remodeling, thereby changing mitochondrial distribution. In addition, neurons are postmitotic cells surviving for the lifetime of the organism. Aged or dysfunctional mitochondria need to be removed from distal axons. Thus, mitochondria alter their motility under certain pathophysiological stress conditions or when their integrity is impaired [5,36]. Defective mitochondrial transport and altered distribution are implicated in the pathogenesis of several major neurodegenerative diseases and neurological disorders [52]. Research into the efficient regulation of mitochondrial trafficking and anchoring in healthy or diseased neurons will advance our knowledge as to how: (1) neurons recruit and redistribute mitochondria to meet altered metabolic requirements; and (2) aged and damaged mitochondria are removed and replenished with healthy ones at distal terminals.

Molecular motors driving neuronal mitochondrial transport

Long-range mitochondrial transport between the soma and distal axonal and dendritic terminals are driven by MT-based motor proteins: kinesin superfamily proteins (KIFs) and cytoplasmic dynein. They mediate long-distance transport of mitochondria and other membranous organelles or cargoes through mechanisms that depend on the polarity and organization of neuronal MTs and require ATP hydrolysis [23,62]. Members of the kinesin-1 family (collectively known as KIF5) are the main motors driving plus end-directed anterograde transport of neuronal mitochondria [24,44,59]. There are three isoforms of KIF5 (KIF5A, KIF5B and KIF5C) in mammals. KIF5B is expressed ubiquitously, whereas KIF5A and KIF5C are only found in neurons [23]. The N-terminus of KIF5 is the motor domain with ATPase and the C-terminal tail is the cargo-binding domain, which links mitochondria via adaptor proteins. Both neuronal imaging and biochemical analyses confirmed that KIF5 motors associate with mitochondria [21,34,44]. Disrupting KIF5-mitochondria coupling in hippocampal neurons impairs mitochondrial transport, thus reducing mitochondrial density in distal axons [4]. Mutation in *Khc*, a kinesin heavy chain in *Drosophila*, disrupts the mitochondrial transport and reduces mitochondrial distribution in larval motor axons [24]. Target disruption of KIF5A or KIF5B in mice also impairs mitochondrial transport and results in perinuclear accumulation of mitochondria [26,59,68]. In addition to KIF5s, two members of the Kinesin-3 family, KIF1B-α and Kinesin-like protein 6 (KLP6), are also involved in regulating mitochondrial transport [39]. Mutant forms of KIF1B-α and KLP6 decrease the mean velocity and density of mitochondria along the axon ([58]; Wozniak et al., 2005). Although Q2 depleting one of them alters the distribution of mitochondria, their role in driving anterograde mitochondrial transport in axons requires further characterization.

Please cite this article as: M.-Y. Lin, Z.-H. Sheng, Regulation of mitochondrial transport in neurons, Exp Cell Res (2015), http://dx.doi.org/10.1016/j.yexcr.2015.01.004