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Update Article

# Regulation of axonal mitochondrial transport and its impact on synaptic transmission

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ABSTRACT

Mitochondria are essential organelles for neuronal survival and play important roles in ATP generation, calcium buffering, and apoptotic signaling. Due to their extreme polarity, neurons utilize specialized mechanisms to regulate mitochondrial transport and retention along axons and near synaptic terminals where energy supply and calcium homeostasis are in high demand. Axonal mitochondria undergo saltatory and bidirectional movement and display complex mobility patterns. In cultured neurons, approximately one-third of axonal mitochondria are mobile, while the rest remain stationary. Stationary mitochondria at synapses serve as local energy stations that produce ATP to support synaptic function. In addition, axonal mitochondria maintain local $Ca^{2+}$ homeostasis at presynaptic boutons. The balance between mobile and stationary mitochondria is dynamic and responds quickly to changes in axonal and synaptic physiology. The coordination of mitochondrial mobility and synaptic activity is crucial for neuronal function synaptic plasticity. In this update article, we introduce recent advances in our understanding of the motor–adaptor complexes and docking machinery that mediate mitochondrial transport and axonal distribution. We will also discuss the molecular mechanisms underlying the complex mobility patterns of axonal mitochondria and how mitochondrial mobility impacts the physiology and function of synapses.

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## 1. Introduction

Proper neuronal function and survival depend upon the supply of appropriate levels of ATP, approximately ninety percent of which is produced by mitochondria via oxidative phosphorylation. Neurons are highly polarized cells whose morphology precludes the efficient diffusion of somally produced ATP to distal processes. While the biogenesis of neuronal mitochondria is not well characterized, it is clear that the majority of mitochondria is produced in the cell body. Thus, distal cellular compartments such as synapses depend upon the efficient delivery of mitochondria through active transport to provide local sources of ATP. Additionally, mitochondria have been shown to aid in critical physiological processes, including the establishment of the axonal resting membrane potential required for action potential propagation, the assembly of the actin cytoskeleton within presynaptic boutons (Lee and Peng, 2008), and the myosin-driven mobilization of synaptic vesicles from the reserve pool to the readily releasable pool during sustained neuronal activity (Verstreken et al., 2005). Furthermore, the ability of mitochondria to buffer $Ca^{2+}$ within presynaptic terminals appears to be involved in certain types of short-term synaptic plasticity (Tang and Zucker, 1997; Billups and Forsythe, 2002; Levy et al., 2003; Kang et al., 2008). Thus, removing mitochondria from axon terminals results in aberrant synaptic transmission (Stowers et al., 2002; Guo et al., 2005; Verstreken et al., 2005; Ma et al., 2009). Many neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis, involve defects in mitochondrial function and transport (see reviews by Chan, 2006; Stokin and Goldstein, 2006).

Mitochondria are transported from the cell body along axonal microtubules (MTs) by protein motors to reach areas with high ATP and calcium buffering requirements like Nodes of Ranvier, axonal branches, active growth cones, and synapses (Fabricius et al., 1993; Morris and Hollenbeck, 1993; Mutsaers and Carroll, 1998; Ruthel and Hollenbeck, 2003; Kang et al., 2008; Zhang et al., 2010). Generally, kinesin motors drive anterograde mitochondrial transport, while dyneins are responsible for retrograde transport (Fig. 1). Individual mitochondrion, however, rarely move in only one direction.

*Abbreviations:* SNPH, syntaphilin; MT, microtubule; KIFs, kinesin superfamily proteins; KHC, kinesin heavy chains; KLC, kinesin light chains; DHC, dynein heavy chains; DIC, dynein intermediate chains; DLIC, dynein light intermediate chains; DLC, dynein light chains; dMiro, *Drosophila* mitochondrial Rho-GTPase; TRAK1, trafficking protein kinesin-binding 1; FEZ1, fasciculation and elongation protein zeta-1; JNK, c-Jun N-terminal kinase; JIP1, c-Jun N-terminal kinase-interacting protein.

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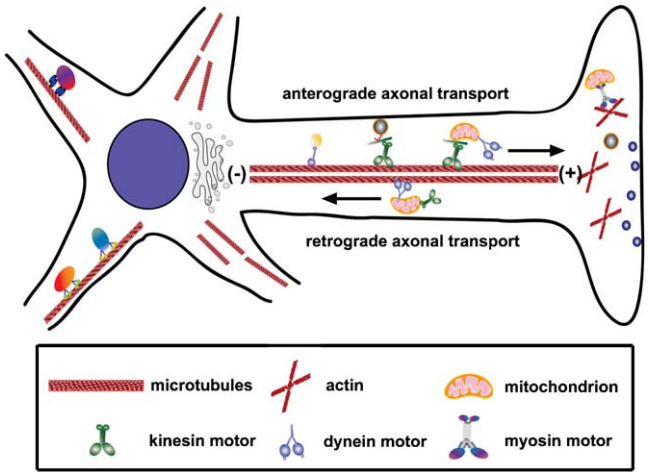


**Fig. 1.** Axonal mitochondrial transport. In axons, MTs are uniformly organized with the plus (+) ends facing toward the axonal terminals and the minus (−) ends toward the cell body. While kinesin motors are mostly plus-end directed, dyneins travel toward the minus ends of MTs. Therefore, kinesin motors generally mediate anterograde axonal transport of mitochondria and dynein drives retrograde axonal transport of mitochondria.

Adapted with permission from Qian Cai, Zu-Hang Sheng. Mitochondrial transport and docking in axons. Experimental Neurology 218, 257-267, 2009.

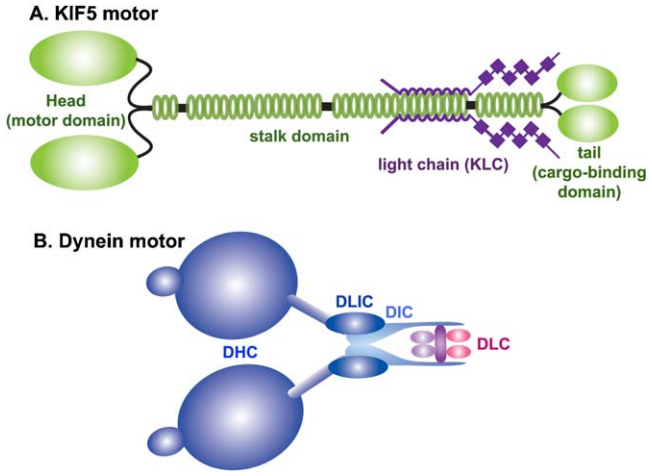


**Fig. 2.** Structure of motor proteins. (A) KIF5 motors form homodimers through the coiled-coil region in the stalk domains. While KIF5 possesses motor function, it also binds to the kinesin-1 light chain (KLC) through its stalk and tail domains. The specific association of KIF5 with cargoes or organelles can be mediated directly through the cargo-binding region in its tail domain or indirectly via the COOH-terminal domains of KLC, indicating the existence of two forms of KIF5 motor-cargo coupling. (B) Cytoplasmic dynein consists of heavy chains (DHC), intermediate chains (DIC), light intermediate chains (DLIC), and light chains (DLC). To transport cargoes, cytoplasmic dynein also bind to the dynactin complex (not shown).

Their transport along MTs typically involves pauses of short and long duration and abrupt changes in direction. At any given time, two-thirds of axonal mitochondria in mature cultured neurons are stationary (Hollenbeck and Saxton, 2005; Kang et al., 2008). Syntaphilin mediates axonal mitochondrial "docking" and helps establish an appropriate axonal mitochondrial distribution (Kang et al., 2008; Chen et al., 2009). The complex mobility patterns of axonal mitochondria may indicate that individual mitochondrion are simultaneously coupled to kinesins, dyneins, and anchoring machinery whose actions compete or oppose one another. Averaging the bidirectional and saltatory components yields a net mitochondrial velocity that falls between fast moving vesicles and slow-moving cytoskeletal proteins: 0.3–2.0 $\mu m\, s^{-1}$ (Morris and Hollenbeck, 1993; Ligon and Steward, 2000).

During development, mitochondrial mobility is tightly regulated to ensure that metabolically active areas are adequately supplied with ATP and able to respond to changes in intracellular $Ca^{2+}$ levels. Later, the structural and functional plasticity characteristic of synapses and axons can drive changes in mitochondrial mobility. For example, the number of immobile mitochondria adjacent to active synapses increases in response to elevated cytosolic $Ca^{2+}$ levels induced by synaptic activity (Rintoul et al., 2003; Yi et al., 2004). It is probable that neuronal development and synaptic activity are partially regulated by the mechanisms that control mitochondrial position. While these events have not been fully elucidated, two prominent proteins have been identified within the last decade. Milton, a *Drosophila* mitochondrial motor adaptor, provides a link between kinesin motors and mitochondria through an interaction with Miro, a calcium-sensing member of the Rho-GTPase family present in the outer mitochondrial membrane (Glater et al., 2006; Saotome et al., 2008; Macaskill et al., 2009; Wang and Schwarz, 2009; Cai and Sheng, 2009). Continued research will produce more regulatory proteins and increase our understanding of how neurons regulate mitochondrial trafficking to maintain synaptic and axonal homeostasis.

## 2. Motor proteins driving axonal mitochondrial transport

ATP-dependent kinesin motors mediate anterograde transport along MT tracks (Hollenbeck, 1996). Since Kinesin-1 (KIF5) was first reported to drive plus end-directed transport *in vitro*, at least 45 different human and mouse kinesin genes have been identified (Hirokawa and Takemura, 2004). Most members of the kinesin superfamily are structurally similar to Kinesin-1 and have two heavy chains (KHCs) and two light chains (KLCs) (Fig. 2A). The heavy chains of Kinesin-1 (KIF5) contain coiled-coil domains that facilitate their association into homo- or heterodimers. Mammals have two neuron-specific KIF5s (KIF5A and -C) and another that is expressed in most cell types (KIF5B) (Kanai et al., 2000, also see review by Hirokawa and Takemura, 2005). The amino terminal domain of each KIF5 contains a MT-binding motor domain, while the carboxyl terminal domain binds to KLCs or interacts directly with cargo adaptors. Thus, through their C-terminal cargo-binding domain, KIF5s attach to cargoes through either a direct interaction between their cargo-binding domains and cargo adaptor proteins or an indirect interaction via their KLCs. Regarding mitochondrial transport, recent studies demonstrate that the former situation is more likely: KIF5s appear to bind mitochondria via their adaptor proteins independent of their KLCs (Cai et al., 2005; Glater et al., 2006).

Several lines of evidence demonstrate that KIF5s play a major role in the anterograde transport of axonal mitochondria (Hurd and Saxton, 1996; Tanaka et al., 1998; Stowers et al., 2002; Cai et al., 2005; Glater et al., 2006). Both imaging and biochemical analyses have confirmed that KIF5 motors associate with brain mitochondria (Hirokawa et al., 1991; Cai et al., 2005; Pilling et al., 2006; Macaskill et al., 2009; Wang and Schwarz, 2009). Furthermore, motor axons of larval *Drosophila kif5* mutants display impaired mitochondrial transport and a reduced mitochondrial distribution (Pilling et al., 2006). In undifferentiated extra-embryonic cells, the targeted disruption of *kif5b* induces aberrant mitochondrial clustering in the perinuclear region as most mitochondria fail to undergo transport toward the cell periphery (Tanaka et al., 1998). Disrupting KIF5-mitochondria coupling in hippocampal neurons by expressing the KIF5 cargo-binding domain transgene induces impaired axonal mitochondrial transport and reduced mitochondrial density in distal axonal compartments (Cai et al., 2005).

Additionally, a member of the kinesin-3 family, KIF1Bα, is widely expressed in the brain and has been shown to inter-

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