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Research report

Conventional kinesin: Biochemical heterogeneity and functional implications in health and disease

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ABSTRACT

Intracellular trafficking events powered by microtubule-based molecular motors facilitate the targeted delivery of selected molecular components to specific neuronal subdomains. Within this context, we provide a brief review of mechanisms underlying the execution of axonal transport (AT) by *conventional kinesin*, the most abundant kinesin-related motor protein in the mature nervous system. We emphasize the biochemical heterogeneity of this multi-subunit motor protein, further discussing its significance in light of recent discoveries revealing its regulation by various protein kinases. In addition, we raise issues relevant to the mode of conventional kinesin attachment to cargoes and examine recent evidence linking alterations in conventional kinesin phosphorylation to the pathogenesis of adult-onset neurodegenerative diseases.

Contents

1. Axonal transport: a specialized form of intracellular trafficking in neurons

Neurons are highly polarized cells bearing morphologically and biochemically distinct somatodendritic and axonal compartments that fulfill information-input and information-output-related functions, respectively (Caceres et al., 2012). Neuritic compartments comprise the overwhelming bulk of the total cell volume of neurons, and some axons may reach lengths of over a meter in humans. The development and life-long maintenance of this unique cellular architecture of neurons involve numerous specializations of the cytoskeleton and the secretory pathway. Together, these specializations facilitate the continuous transport and delivery of molecular components from their place of synthesis and packaging in the neuronal cell body to specialized subdomains within dendrites and axons (Bradke and Dotti, 2000; Higgins et al., 1997; Maeder et al., 2014; Morfini et al., 2001).

Intracellular directional transport of membrane-bounded organelles (MBOs) is driven by molecular motors, mechanochemical proteins that utilize energy derived from ATP hydrolysis to translocate their cargoes along specific filamentous components of the neuronal cytoskeleton (Hirokawa et al., 2010). Short-range

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transport of MBOs within actin filament-rich cellular domains, including growth cones, pre- and post-synaptic terminals, is mainly powered by the *myosin* family of motor proteins (Kneussel and Wagner, 2013). On the other hand, long-range transport of MBOs from their site of assembly and packaging (*i.e.*, the *trans* Golgi network) to specific dendritic and axonal compartments is mediated by microtubule-based molecular motors (Hirokawa et al., 2009).

2. Microtubule-based motor proteins power axonal transport

Microtubules are intrinsically polarized, with beta-tubulin being present at the plus-end and alpha-tubulin at the minus-end (Baas et al., 2016). The intrinsic polarity of microtubules is recognized by molecular motor proteins, and allows for directional transport of cargoes along the microtubule surface. Within axons, microtubules are mostly uniformly oriented, with their plus ends directed towards the presynaptic terminals. This microtubule organization within axons allows for transport of MBOs in the retrograde (from the cell periphery towards the cell soma) and anterograde (away from the neuronal soma) directions (Black, 2016; Morfini et al., 2012). The former mainly depends on the large multisubunit motor protein *cytoplasmic dynein*, whereas anterograde AT is executed by the kinesin superfamily of motor proteins (KIFs) (Hirokawa and Noda, 2008). Unlike axons, microtubules in vertebrate dendrites display a non-uniform (mixed) orientation. Accordingly, unidirectional motor proteins could, in principle, move cargoes away and towards the neuronal soma within this subcompartment (Baas et al., 2016).

Microtubule motor-based intracellular trafficking of molecular components within axons represents a cellular process collectively referred to as *axonal transport* (AT) (Black, 2016). AT involves the delivery of components synthesized in the neuronal soma to specific axonal subdomains, the removal of old and damaged cellular components from these domains, and the sustained maintenance of neurotrophic support [reviewed in (Black, 2016; Morfini et al., 2012)]. As such, AT is regarded as a cellular process critical for the appropriate maintenance of neuronal architecture and connectivity throughout the long lifetime of neurons (Brady and Morfini, 2010; Morfini et al., 2009a).

In mammals, the KIF superfamily of motors comprises 45 different genes, of which 38 are expressed in nerve tissue (Miki et al., 2003). Based on phylogenetic analysis and sequence homology, KIF members have been classified into 15 KIF subfamilies, termed kinesin-1 to kinesin-14B (Lawrence et al., 2004). Closer sequence similarities within members of each KIF subfamily have long been thought to reflect related functionalities, but the specific function of most KIFs has yet to be established. While a possibility exists that each MBO type is transported by a unique KIF, the number of KIFs expressed in nerve tissue largely exceeds the number of defined MBO cargoes, and only a few KIFs have been confirmed to mediate AT of specific MBOs in neurons, suggesting that some cellular activities requiring KIFs may have not yet been recognized (Brady and Sperry, 1995). Moreover, cumulative evidence also suggests functional redundancy among some KIF members on the AT of some MBOs, particularly mitochondria (Saxton and Hollenbeck, 2012). Here, we focus our review on basic aspects of *conventional kinesin*, the founding member of the KIF superfamily of proteins, and the most abundant KIF in the mature mammalian nervous system (Wagner et al., 1989).

3. Conventional kinesin: structural organization and biochemical diversity

Conventional kinesin was initially purified from mammalian brain tissue taking advantage of its unique biochemical properties,

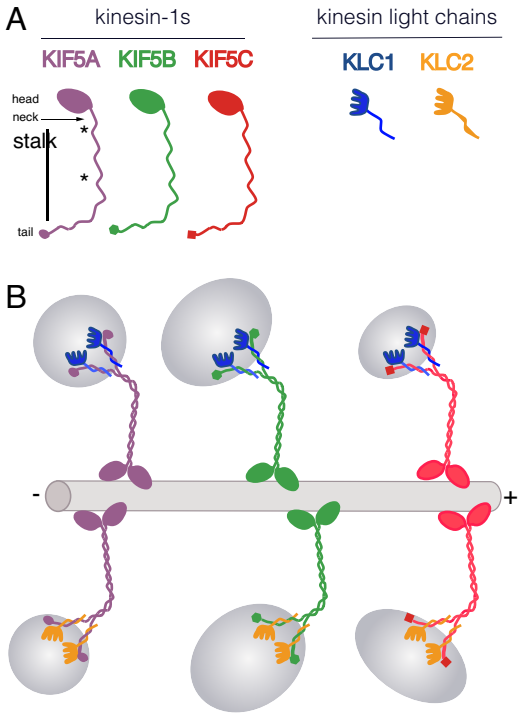

Fig. 1. Conventional kinesin subunit variants. (A) Three kinesin-1 genes are expressed in mammalian tissues, including the neuron-enriched KIF5A and KIF5C isoforms, and the ubiquitously expressed KIF5B isoform. The overall structure of KIF5s is highly conserved, involving a head domain responsible for microtubule binding and ATP hydrolysis, a neck linker region, and a long stalk mainly comprising coiled-coil and hinge domains (asterisks) involved in KIF5 homodimerization. The globular tail domain of KIF5 features the most divergent sequences among KIF5 subunits. (B) Biochemical experiments demonstrated that both KIF5s and KLCs are present as homodimers within the conventional kinesin holoenzyme. Combinations of KIF5 and KLC homodimers give rise to six conventional kinesin variants, as defined by their subunit composition. Alternative splicing of the carboxy terminal region of KLC1 further increases the complexity of these variants. Experimental evidence suggests combined roles of the tail domain of KIF5s and the carboxy terminus of KLCs on the targeting of conventional kinesin variants to MBOs of unique protein composition.

which were first revealed by pioneering microscopic observations in the isolated squid axoplasm preparation (Allen et al., 1982; Brady, 1985; Brady et al., 1983; Vale et al., 1985). To date, it is well established that this motor protein exists as a heterotetrameric complex of approximately 380 kDa, being composed of two *kinesin heavy chain* subunits of 115–130 kD, and two *kinesin light chain* (KLCs) subunits of 62–70 kD (Wagner et al., 1989) (Fig. 1).

After standardization of the kinesin nomenclature (Lawrence et al., 2004), heavy chain subunits of conventional kinesin were listed as members of the *kinesin-1* subfamily of KIFs. A single kinesin-1 gene is encoded in the *Caenorhabditis elegans* (UNC-116) and *Drosophila melanogaster* genomes, with genetic deletion experiments indicating an essential role of this subunit on organism development and synaptic function (Hurd and Saxton, 1996; Siddiqui, 2002). In contrast, the mammalian kinesin-1 subfamily comprises three genes encoding the neuron-enriched *KIF5A* and *KIF5C*, and the ubiquitously expressed *KIF5B* members (Kanai et al., 2000) (Fig. 1A). Immunoelectron microscopy-based visualization of the purified conventional kinesin holoenzyme revealed kinesin-1 subunits as two 80 nm long rods, each featuring a globular head and a fan-shaped tail (Bloom et al., 1988; Hirokawa et al., 1989). A molecular basis underlying this structure was illuminated after KIF5 protein sequences became available (Kosik et al., 1990), and it is now clear that the overall protein domain organization of all KIF5 members within the kinesin-1 subfamily is highly conserved [reviewed in (Jeppesen and Hoerber, 2012)]. A head motor region,