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Review

Neurobiology of axonal transport defects in motor neuron diseases: Opportunities for translational research?

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ABSTRACT

Intracellular trafficking of cargoes is an essential process to maintain the structure and function of all mammalian cell types, but especially of neurons because of their extreme axon/dendrite polarisation. Axonal transport mediates the movement of cargoes such as proteins, mRNA, lipids, membrane-bound vesicles and organelles that are mostly synthesised in the cell body and in doing so is responsible for their correct spatiotemporal distribution in the axon, for example at specialised sites such as nodes of Ranvier and synaptic terminals. In addition, axonal transport maintains the essential long-distance communication between the cell body and synaptic terminals that allows neurons to react to their surroundings via trafficking of for example signalling endosomes.

Axonal transport defects are a common observation in a variety of neurodegenerative diseases, and mutations in components of the axonal transport machinery have unequivocally shown that impaired axonal transport can cause neurodegeneration (reviewed in El-Kadi et al., 2007, De Vos et al., 2008; Millecamps and Julien, 2013). Here we review our current understanding of axonal transport defects and the role they play in motor neuron diseases (MNDs) with a specific focus on the most common form of MND, amyotrophic lateral sclerosis (ALS).

Contents

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1. Microtubule-based axonal transport

Traditionally two main classes of axonal transport are distinguished based on the overall speed of movement, namely fast axonal transport (~50–400 mm/day or 0.6–5 μm/s) and slow axonal transport (0.2–10 mm/day or 0.0002–0.1 μm/s). Slow axonal transport is further subdivided into slow component a (SCa) and b (SCb) based on the proteins transported and the speed, 0.2–3 and 2–10 mm/day, respectively. We now know that both fast and slow axonal transport is mediated by the same molecular motors that move cargoes along microtubules, with the differences in overall speed caused by prolonged pauses between movement phases in slow axonal transport (reviewed in Black, 2016).

Microtubules are polymers made up of tubulin which itself is a heterodimer of α-tubulin and β-tubulin. Microtubules are rigid hollow rods of approximately 25 nm in diameter built from 13 linear protofilaments composed of alternating tubulin heterodimers and arranged around a hollow core. Due to the head to tail arrangement of the tubulin heterodimers microtubules are polarised with a fast growing plus end and a slow growing minus end. The polarity of microtubules dictates the direction of movement of the molecular motors along them.

There are two major families of microtubule based molecular motors, namely the kinesin family which move mostly toward the plus end of microtubules and the cytoplasmic dyneins that move toward the minus end (reviewed in Hirokawa et al., 2010). Because axonal microtubules are uniformly orientated with their plus end pointing away from the cell body (Baas et al., 1988) kinesins mediate anterograde transport away from the cell body toward the axon terminal and cytoplasmic dynein drives retrograde transport from the distal axon toward the cell body.

The human kinesin superfamily contains 45 members, subdivided into 15 subfamilies. The main kinesin family members involved in fast axonal transport are kinesin-1 (previously referred to as conventional kinesin or KIF5), and the kinesin-3 family members KIF1A, KIF1Bα and KIF1Bβ. Anterograde slow axonal transport appears to be mainly mediated by kinesin-1 (Xia et al., 2003). Kinesin-1 is a heterotetramer consisting of two kinesin heavy chains (KHCs) and two kinesin light chains (KLCs). KHC contains the catalytic motor domain, a neck linker region, an α-helical stalk interrupted by two hinge regions, and the tail. The motor domain binds microtubules and hydrolyses ATP to generate force. Together with the neck region, the motor domain conveys processivity and direction of movement. The stalk is required for dimerisation and the tail, together with KLC is involved in regulation of motor activity as well as cargo binding (reviewed in Hirokawa et al., 2010). The latter also involves various adapter proteins such as c-Jun N-terminal kinase (JNK)-interacting protein (JIP) 1, 3 and 4, mitochondrial Rho GTPase (Miro) 1 and 2, trafficking kinesin (TRAK) 1 and 2, and huntingtin that link kinesin-1 to specific cargo, directly or via KLCs (reviewed in Fu and Holzbaur, 2014). In contrast to kinesin-1, KIF1A and KIF1Bα/β are monomeric kinesin motors consisting of an N-terminal motor domain, a conserved stalk domain and a C-terminal pleckstrin homology (PH) that aids in the interaction with cargoes in conjunction with adapter proteins such as DENN/MADD (Differentially Expressed In Normal And Neoplastic Cells/MAP Kinase Activating Death Domain) (Niwa et al., 2008). Kinesin-1 transports a number of different fast axonal transport cargoes including mitochondria and a variety of vesicular and non-vesicular cargoes such as lysosomes, signalling endosomes (e.g. brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase (Trk) B (TrkB) vesicles), amyloid precursor protein (APP) vesicles, AMPA vesicles, and mRNA/protein complexes. Kinesin-1 also mediates the slow axonal transport of cytoskeletal cargoes such as microtubules and neurofilaments (reviewed in Hirokawa et al., 2010). KIF1A and KIF1Bβ motors transport synaptic vesicle precursors (Okada et al., 1995), signalling endosomes such as TrkA vesicles (Tanaka et al., 2016), and the autophagy protein ATG9 (Stavoe et al., 2016). KIF1Bα has also been proposed to drive anterograde transport of mitochondria (Nangaku et al., 1994).

In contrast to the multiple kinesins that drive anterograde transport, retrograde transport is almost exclusively mediated by a single cytoplasmic dynein. Cytoplasmic dyneins are members of the ATPases associated with diverse cellular activities (AAA+) family of ATPase proteins. They are sub-divided into cytoplasmic dynein 1 and 2, with cytoplasmic dynein 1 being the main retrograde molecular motor in neurons. Cytoplasmic dynein 1 (hereafter referred to as dynein) is composed of two homodimerised dynein heavy chains (DHCs) and multiple dynein intermediate (DIC), dynein light intermediate (DLIC), and light chains (LC) (reviewed in King, 2012). The assembly of these polypeptides forms a ~1.5 MDa protein complex whose functions, cargo binding and localisation are regulated by adapter complexes including dynactin, Bicaudal D2 (BICD2), lissencephaly 1 (LIS1), nuclear distribution protein (NUDE or NDE) and NUDE-like (NUDEL or NDEL). The ~1 MDa dynactin complex contains p150Glued which interacts with a short actin-like Arp1 filament and various additional dynactin subunits including p50/dynamitin, p62, CapZ, p27, p25, and p24. p150Glued associates with dynein via the DICs and also directly binds to microtubules; through its cargo-binding domain p150Glued binds a number of vesicular cargo adapters, including sorting nexin 6 (SNX6), huntingtin-associated protein 1 (HAP1) and JIP1 (reviewed in Kardon and Vale, 2009; Fu and Holzbaur, 2014).

2. Axonal transport defects in ALS

ALS, the most common form of MND, is an adult onset and progressive neurodegenerative disorder caused by selective injury and death of upper motor neurons in the motor cortex and lower motor neurons in the brain stem and spinal cord. Degeneration of motor neurons leads to progressive muscle wasting followed by paralysis and usually culminates in death through respiratory failure. ALS has an incidence of 2 per 100,000 and a mean age of onset of 55–65 years. The average survival is approximately 3 years from symptom onset (reviewed in Kiernan et al., 2011). An estimated 10% of ALS is inherited, usually in an autosomal dominant fashion (familial ALS), but most ALS cases have no clear genetic basis and occur seemingly random in the population (sporadic ALS). Several genes have been associated with familial ALS, including *superoxide dismutase 1* (*SOD1*) (~12% of familial cases), *TAR DNA binding protein* (*TARDBP*; TDP-43) (~4%), *Fused in sarcoma* (*FUS*) (~4%), and *C9orf72* (~40%) (reviewed in Renton et al., 2014). The causes of motor neuron degeneration appear multifactorial. From research mostly on familial ALS cases and animal models a number of possible pathogenic mechanisms underlying motor neuron degeneration have emerged including oxidative stress, mitochondrial dysfunction, misfolded protein toxicity/autophagy defects, RNA toxicity, excitotoxicity, and defective axonal transport (reviewed in Ferraiuolo et al., 2011; De Vos et al., 2008; Millecamps and Julien, 2013).