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Review article

The cytoskeleton as a novel therapeutic target for old neurodegenerative disorders

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ABSTRACT

Cytoskeleton defects, including alterations in microtubule stability, in axonal transport as well as in actin dynamics, have been characterized in several unrelated neurodegenerative conditions. These observations suggest that defects of cytoskeleton organization may be a common feature contributing to neurodegeneration. In line with this hypothesis, drugs targeting the cytoskeleton are currently being tested in animal models and in human clinical trials, showing promising effects. Drugs that modulate microtubule stability, inhibitors of posttranslational modifications of cytoskeletal components, specifically compounds affecting the levels of tubulin acetylation, and compounds targeting signaling molecules which regulate cytoskeleton dynamics, constitute the mostly addressed therapeutic interventions aiming at preventing cytoskeleton damage in neurodegenerative disorders. In this review, we will discuss in a critical perspective the current knowledge on cytoskeleton damage pathways as well as therapeutic strategies designed to revert cytoskeleton-related defects mainly focusing on the following neurodegenerative disorders: Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis and Charcot-Marie-Tooth Disease.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; ABP, actin binding protein; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; Aβ, amyloid-β; Cdk5, cyclin-dependent kinase 5; CMT, Charcot-Marie-Tooth disease; CMT2, Charcot-Marie-Tooth disease type 2; CRMP-2, collapsin response mediator protein 2; Epo, Depothilone D; GSK3β, glycogen synthase kinase 3β; HD, Huntington disease; HDAC6, histone deacetylase 6; HSP, hereditary spastic paraplegia; KIF, kinesin superfamily; LKE, lanthionine ketamine ester; MAP, microtubule associated protein; MAP1B, microtubule associated protein 1B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimide; MT, microtubule; NFT, sneurofibrillary tangles; PD, Parkinson's disease; SIRT-2, sirtuin-2; SOD1, superoxide dismutase 1.

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1. The neuronal cytoskeleton

Neurons are amongst the most highly polarized cells containing two distinct functional compartments, the axonal and the somatodendritic compartment (Craig and Banker, 1994). The axon is a unique projection that functions as a signal transmitter, which contacts with neighboring cells conveying the electric impulse and neuronal information. The somatodendritic compartment is composed by the neuronal cell body and multiple branched dendrites which receive signals. The neuronal cytoskeleton is crucial in maintaining this asymmetric shape and polarity, since it provides not only the neuronal structural backbone, but also because it separates functionally the two different compartments (Witte and Bradke, 2008). Axons can extend to remarkable distances (up to 1 m in humans), which raises the need of a well-constructed machinery that shuttles vital cellular components from the cell body along the axonal projection (Kapitein and Hoogenraad, 2011). As such, an appropriately organized neuronal cytoskeleton is needed during nervous system development, maintenance and also during regenerative processes that follow injury. The maintenance of the neuronal structural integrity requires controlled internal organization of its three cytoskeletal components: the intermediate filaments, actin microfilaments and microtubules (Kapitein and Hoogenraad, 2015; Luo, 2002; Yuan et al., 2012). Of note, these cytoskeleton components are shaped by proteins that can be assembled in a wide combination of ways, giving rise to different structures with different properties, and that can also be disassembled and reassembled into different shapes according to the specific spatio temporal needs (Fletcher and Mullins, 2010).

1.1. Neuronal cytoskeleton components: the building blocks of polarity

The neuronal cytoskeleton is composed by intermediate filaments (IFs), actin filaments, and microtubules (MTs). IFs constitute the largest family of mammalian cytoskeleton proteins and they provide mechanical strength and stabilize the cytoskeleton framework. In adult neurons, 5 types of IFs are expressed: the type IV neurofilament (NF) triplet proteins (NF-light (NF-L), NF-medium (NF-M) and NF-heavy (NF-H)) (Shaw and Weber, 1982), α-internexin (Fliegner et al., 1994) and the type III peripherin (Troy et al., 1990). Each IF subunit is composed by a globular N-terminal head, a α-helical rod domain, and variable C-terminal tail domains that differ in length and amino acid composition. Neuronal IF assembly starts with the formation of parallel, side-to-side, coiled-coil dimers of IF subunits, mediated by the association of their rod domains. Subsequently, two dimers line up in an anti-parallel manner, forming a tetramer. Aggregates formed by approximately eight tetramers constitute a unit-length-filament (ULF) of approximately 55 nm in length (Herrmann et al., 1999; Hisanaga and Hirokawa, 1988). Elongation occurs through the axial aggregation of ULFs forming immature filaments of about 16 nm in diameter and many microns in length. Finally, radial compaction takes place resulting in packing of the filaments to constitute the final 10 nm filament. Filaments are lengthened by dynamically joining ends of shorter filaments. The core of the filaments is composed by the rod domains while the C-terminal tails form flexible extensions that link the filaments to each other and to other elements in the cytoplasm (Uchida et al., 2013). NF assembly is regulated by post-translational modifications namely phosphorylation of the N-terminal head domain (Sihag and Nixon, 1989, 1990) which in the case of NF-L inhibits its assembly suggesting that this modification has a role in maintaining NFs in a disassembled state (Hisanaga et al., 1990). The NF head phosphorylation occurs in the cell body and is reverted for its assembly and transport along the axon where NFs exert their function (Nixon and Lewis, 1986 Sihag and Nixon, 1991). The C-terminal tail of NFs, namely of NF-M and NF-H, is also phosphorylated in a spatially regulated manner. In the cell body NFs have predominantly non-phosphorylated tails which become extensively phosphorylated in mature axons (Nixon and Logvinenko, 1986; Sihag and Nixon, 1990). Phosphorylation of the tail of NFs is important for the interaction between NF domains themselves and also for their interaction with MTs (Hisanaga and Hirokawa, 1989; Hisanaga et al., 1991). Moreover, tail phosphorylation confers NFs resistance to proteolysis (Pant, 1988).

The actin cytoskeleton is composed of actin monomers (G-actin) that have tight binding sites that enable head-to-tail interactions with two other actin monomers, such that they polymerize to form thin, flexible actin filaments (F-actin) of approximately 7 nm in diameter (Spudich et al., 1972). These filaments are organized into higher-order structures, forming bundles or three-dimensional networks. Since the actin monomers are oriented in the same direction, actin filaments display polarity with distinguishable plus and minus ends. The reversible addition of monomers happens in both ends, but the plus end elongates five to ten times faster than the minus end (Pollard and Mooseker, 1981). Actin monomers bind ATP, which leads to a faster polymerization and ATP is then hydrolyzed to ADP after assembly (Hayashi and Rosenbluth, 1962; Offer et al., 1972). In neurons, actin is seen as the engine behind the generation of the force necessary to regulate the neuronal shape and cellular internal and external movements (Luo, 2002).

MTs are parallel bundles of protofilaments of α- and β-tubulin which play a significant role in cellular structure since they function as architectural backbones for neurons being crucial to maintain axonal integrity and form the tracks for axonal transport (Prokop, 2013). Both α-tubulin and β-tubulin bind to GTP that regulates polymerization. Shortly after polymerization GTP is hydrolyzed and the affinity of tubulin for adjacent molecules weakens, favoring depolymerization and resulting in the dynamic state characteristic of MTs (Mitchison and Kirschner, 1984). MTs also undergo treadmilling, a dynamic process in which the plus end of the filament grows in length while the other one shrinks, due to the removal of tubulin molecules bound to GTP from the minus end that travel to the plus end of the same MT (Walker et al., 1988). In many cell types, MTs are nucleated at the centrosomal region in the microtubule-organizing center (MTOC) which is the starting point of MT polymerization where α- and β-tubulin dimers associate with a previously formed γ-tubulin ring and start elongating from there (Joshi et al., 1992; Sunkel et al., 1995). Yet, neurons have the ability to be centrosomal independent regarding MT nucleation. Studies using *Drosophila* neurons demonstrated that in the absence of functional centrosomes, neurons developed a normal MT network and a healthy axonal outgrowth (Basto et al., 2006; Nguyen et al., 2011). Moreover, another recent study using rat hippocampal neurons evidenced that centrosomes lose their MTOC function during neuronal development and that axon