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REVIEW

Cytoskeletal changes in diseases of the nervous system

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Abstract **The neuronal cytoskeleton not only provides the structural backbone of neurons, but also plays a fundamental role in maintaining neuronal functions. Dysregulation of neuronal architecture is evident in both injury and diseases of the central nervous system. These changes often result in the disruption of protein trafficking, loss of synapses and the death of neurons, ultimately impacting on signal transmission and manifesting in the disease phenotype. Furthermore, mutations in cytoskeletal proteins have been implicated in numerous diseases and, in some cases, identified as the cause of the disease, highlighting the critical role of the cytoskeleton in disease pathology. This review focuses on the role of cytoskeletal proteins in the pathology of mental disorders, neurodegenerative diseases and motor function deficits. In particular, we illustrate how cytoskeletal proteins can be directly linked to disease pathology and progression.**

Keywords cytoskeleton, actin, microtubules, intermediate filaments, nervous system, disease

Introduction

The direct impact that cell morphology has on cellular function is reflected by the vast variety of neuronal cell types with distinct morphologies. The architecture of neurons not only provides structure to cells but serves many physiological functions such as cell motility, endocytosis, the transport of organelles and helps maintain the correct directional flow of signal transmission. The neuronal cytoskeleton is comprised of three interconnected structural filament systems, actin microfilaments, intermediate filaments and microtubules.

The support of neuron-specific functions, such as axonal transport and synaptic signaling, by the cellular architecture can only be achieved if all components of the cytoskeleton are properly maintained. Dysfunction of the neuronal cytoskeleton is involved in a variety of diseases including mental disorders, neurodegenerative diseases and motor function deficits, highlighting the importance of the cytoskeleton for the normal function of neurons. Although some of the cytoskeletal changes observed in neurodegenerative diseases may be a side-effect that is not directly involved in the pathological process, many neurological disorders involve the breakdown of cellular architecture at the synapse, which results in disrupted neuronal communication. For example, both epilepsy and schizophrenia are associated with the disassembly of filament systems resulting in the loss of neuronal cell structure and subsequent deterioration in signal transmission. The accumulation of proteins, as seen in most neurodegenerative diseases, is known to disrupt the normal functioning of cytoskeletal networks. In this review, we outline the components of the cytoskeleton, their neuron specific roles and how these roles are affected in the diseased state.

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Structure of the cytoskeleton

Actin microfilaments

Actin is a 42 kDa globular protein and is the major component of the microfilament cytoskeleton. There are six different actin genes, which give rise to six distinct isoforms; with β_{cyto}-actin and and γ_{cyto}-actin isoforms building the actin cytoskeleton of non-muscle cells. Actin filaments (F-actin) are formed by the polymerization of globular actin (G-actin), which kinetically favors the formation of filaments via an initial nucleation step (Mitchison and Cramer, 1996). F-actin is polarized: with the fast growing (barbed) ends and the slow

growing (minus) ends having distinct rates of assembly and disassembly.

A number of actin binding proteins (ABPs) regulate actin filament dynamics. Nucleating factors, such as formins and Arp2/3, aid in the nucleation of actin into filaments and the formation of branched networks. Profilin is involved in the polymerisation of G-actin to F-actin by providing new actin subunits to the barbed ends. The complex arrangement of actin filament networks is achieved by proteins that bundle (e.g. fascin) or cross link (e.g. α-actinins and filamins) actin filaments (Mockrin and Korn, 1980; Tseng et al., 2004; Bugyi et al., 2006; Korobova and Svitkina, 2008). Tropomyosins, which form a polymer along the α-helical groove of the actin filament, regulate actin dynamics by both interacting with other ABPs and via direct interactions of different tropomyosin isoforms with the actin filament (Gunning et al., 2008; Schevzov et al., 2012). Although cofilin is typically classed as an actin severing protein, the concentration of active cofilins within the cell determines the effect cofilin has on actin. Typically, low concentrations of active cofilins favor stabilization, intermediate levels favor severing and at high cofilin to actin subunit ratios, cofilin can nucleate actin filaments (Andrianantoandro and Pollard, 2006; Kuhn and Bamburg, 2008). Cofilin activity is regulated by phosphorylation at the Ser3 residue. Phosphatases, such as Slingshot phosphatase, activate cofilin while kinases, such as LIM-kinase1 (LIMK1), inactivate cofilin (Arber et al., 1998; Yang et al., 1998; Niwa et al., 2002). Therefore, levels of cofilin phosphorylation are often measured to determine the degree of cofilin activity.

Neurons in most regions of the brain display small protrusions, known as dendritic spines. Dendritic spines are the primary target for excitatory synaptic input within the brain. In mature neurons, actin shows strong enrichment in dendritic spines (Cohen et al., 1985) and forms a meshwork of F-actin (Luo et al., 1996). This network anchors postsynaptic receptors and signaling molecules, which are necessary for long-term potentiation (LTP) and depression (LTD) (Kim and Lisman, 1999; Bosch and Hayashi, 2012). Indeed, an increase in F-actin has been shown after tetanus-induced LTP in the diffuse cytoskeletal meshwork that connects the dendritic cytoplasm to the spine matrix (Pavlik and Moshkov, 1991). By contrast, LTD induces a shift in the ratio of G-actin/F-actin toward G-actin, therefore decreasing actin filaments in spines, resulting in spine shrinkage (Okamoto et al., 2004). The dynamic nature of dendritic spines is made possible by the actin cytoskeleton and the associated actin binding proteins (Luo et al., 1996; Okamoto et al., 2004). Disruption of the actin cytoskeleton has been shown to result in global disassembly of synaptic structural elements. In particular, it has been shown that F-actin is a likely target for stimuli that drive either synaptic stability or elimination (Zhang and Benson, 2001) and alterations in the actin cytoskeleton have adverse effects on dendritic spines, both in the ultrastructure of the individual spines and on the number and distribution of spines along dendrites.

Intermediate filaments

Intermediate filaments (IF) are the largest family of cytoskeletal proteins in mammalian cells and are differentially expressed in neurons, based on developmental state and localization within the nervous system. They function in regulating axonal diameter, neuronal differentiation, axon outgrowth and regeneration (Zhu et al., 1997). Five types of IFs are expressed in adult neurons; three types of neurofilaments (NF), α-internexin and peripherin. NFs are neuron specific, type IV IFs and include NF-L (light) NF-M (medium) and NF-H (heavy). All NFs share a homologous central rod domain spanning 310 amino acid residues, which forms a highly conserved α-helical domain that is responsible for the formation of a coiled-coil structure. On either side of the central rod domains, the amino- (head) and carboxy (tail)-terminal regions are located. These end domains are structurally and functionally distinct between IF proteins with dramatic differences in size between NF-L (67 kDa), NF-M (150 kDa) and NF-H (200 kDa) due to differences in the C-terminals. IFs form an antiparallel tetramer, consisting of two α-helical chains, which are aligned parallel and intertwined to form a coiled-coil rod. Eight tetramers are packed together to form an intermediate filament (Fuchs and Cleveland, 1998). IFs are unique in their assembly. Whereas actin filament and microtubule assembly occurs from either end of the filament, intermediate filament assembly occurs along the whole filament, whereby exchange between the subunits of the monomeric and filamentous pools occurs. Mutations in NFs have been reported in numerous diseases including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth disease, giant axonal neuropathy and spinal muscular atrophy (Perrot et al., 2008), indicative of the importance of NF stability in the functioning of healthy neurons (for a detailed review, see also Cairns et al., 2004). The formation of cytoplasmic inclusion containing intermediate filament aggregates also define a group of neurodegenerative disorders classed as neuronal intermediate filament inclusion disease (NIFID, Armstrong et al., 2006). The characteristic feature of these inclusions and their comparison to other cytoplasmic inclusions, found in neurodegenerative diseases have been studied and discussed comprehensively elsewhere (Armstrong and Cairns, 2012).

Microtubules

Microtubules, the cytoskeletal polymer with the largest diameter, are cylindrical protein filaments. They are comprised of α- and β- tubulin heterodimer subunits, which are 8 nm in length. The polar organization of microtubules is

generated by the assembly of 13 α-/β-tubulin dimers, which interact both laterally and longitudinally, leading to the formation of a faster growing (plus) and slower growing (minus) end (Downing and Nogales, 1998). Microtubules exhibit a polar filament organization which is important for morphogenesis, axonal extension and the transport of vesicles and proteins; allowing signaling molecules, trophic factors and other cellular constituents (such as organelles) to travel along the axon (Roy et al., 2005).

Like actin filaments, microtubules are associated with a number of proteins that bind and regulate microtubule dynamics (Dehmelt and Halpain, 2004). Microtubule-associated proteins (MAPs) are a family of proteins that regulate microtubule dynamics. They are differentially compartmentalized in neurons with MAP2 being primarily localized to the soma and dendrites, while tau is predominantly found in the axons of neurons where it functions to stabilize and assemble microtubules (Bloom and Vallee, 1983; Bernhardt and Matus, 1984; Lee et al., 2001). Dysfunction of the tau protein has been implicated in numerous neurodegenerative diseases termed tauopathies. The identification of pathogenic mutations, both exonic and intronic, in the tau gene in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) suggests that tau dysfunction is sufficient to cause neurodegeneration on its own (Hutton et al., 1998).

The tight regulation of cytoskeletal proteins is important for the normal functioning of the nervous system. There is increasing evidence that abnormalities in cytoskeletal proteins cause neurological diseases. In particular, mutations in several filament proteins are now associated with neurological diseases. The following sections discuss how all three filament systems impact on the development of disease in developing neurons, mature neurons of the central nervous system and in motor neurons (see Fig. 1).

Neurological disorders

Schizophrenia

Schizophrenia is a psychiatric illness associated with deficits in neuronal connections and synapse alteration. Post mortem schizophrenia brains are commonly characterized by reduced dendritic spine density (Garey et al., 1998; Glantz and Lewis, 2000, 2001; Sweet et al., 2009). As the actin cytoskeleton is involved in the formation and maintenance of dendritic spines (Okamoto et al., 2004), it is postulated that molecular pathways involved in the stabilization of actin filaments may be abnormal in schizophrenia (Hill et al., 2006; Rubio et al., 2012).

There is increasing evidence that Rac-Pak signaling is affected in schizophrenia (Rex et al., 2009; Rubio et al., 2012; Deo et al., 2013). The Rac-PAK signaling pathway is critical to long-term stabilization of the actin cytoskeleton, with disruption of either Rac or PAK increasing the vulnerability of LTP (Rex et al., 2009). Both Rac and CDC 42 regulate PAK1. Investigations into the Rac-PAK pathways revealed reduced levels of kalirin, an essential regulator of synapse formation (Schevzov et al., 2012)and CDC42 mRNA in the gray matter of subjects with schizophrenia (Hill et al., 2006). Furthermore, dendritic spine number and morphology has been shown to be influenced by kalirin (Xie et al., 2007) while CDC42 is associated with filopodia formation and actin stabilization (Bishop and Hall, 2000). GTP-bound Rac and CDC42 activate PAK1 (Manser et al., 1994), which transphosphorylates and activates Lim kinase-1 (LIMK-1), phosphorylating and thereby inactivating cofilin, so that it cannot depolymerise F-actin (Edwards et al., 1999). As schizophrenia patients exhibit reduced CDC42, this would be expected to result in decreased PAK1 activation, increased activation of cofilin and depolymerisation of F-actin in dendritic spines. However, PAK1 levels have been shown to be unchanged in the auditory cortex (Deo et al., 2013) but increased in the dorsolateral prefrontal cortex (Rubio et al., 2012) in subjects with schizophrenia.

PAK1 knockout mice exhibit dramatically reduced LTP along with normal spine and synaptic structures. However, they present with reduced spine F-actin and phosphorylated cofilin, suggesting that PAK1 affects hippocampal LTP via F-actin and cofilin without morphological changes (Asrar et al., 2009). These findings are contradicted by dominant negative (dnPAK1) transgenic mice, which are characterized by enhanced LTP and basal synaptic responses in the cortex (Hayashi et al., 2004). Although further investigations are necessary, both murine and human studies suggest that the PAK1 pathway may be disrupted in certain brain regions in schizophrenia patients and that disruption of signaling to the actin cytoskeleton in the postsynaptic compartment has major implications in the pathology of schizophrenia.

Schizophrenia is also associated with changes in NFs. An increase of 25%–30% in NF-L mRNA was observed in the thalamus of schizophrenia patients (Clinton et al., 2003). It has been suggested that NF-L may impact on NMDA receptor localization to the postsynaptic density by interacting with the cytoplasmic C-terminal domain of NR_1 subunits in NMDA receptors (Ehlers et al., 1995; Ehlers et al., 1998). Investigations into expression levels of other NF subunits revealed elevated levels of NF-M transcripts, but NF-H levels were unchanged (Clinton et al., 2004). This suggests that alterations in NFs may impact on the regulation of neurotransmission, although changes in NFs at the protein level are yet to be determined in schizophrenia.

The involvement of MAPs in schizophrenia is still largely unresolved. Post-mortem studies reveal upregulation of MAP6 and MAP2 in the prefrontal cortex of schizophrenia patients with suggestions that MAP6 may be involved in the cytoskeletal changes observed in schizophrenia (Anderson et al., 1996; Cotter et al., 2000; Shimizu et al., 2006). However, suppression of MAP6 in mice causes depletion of vesicle

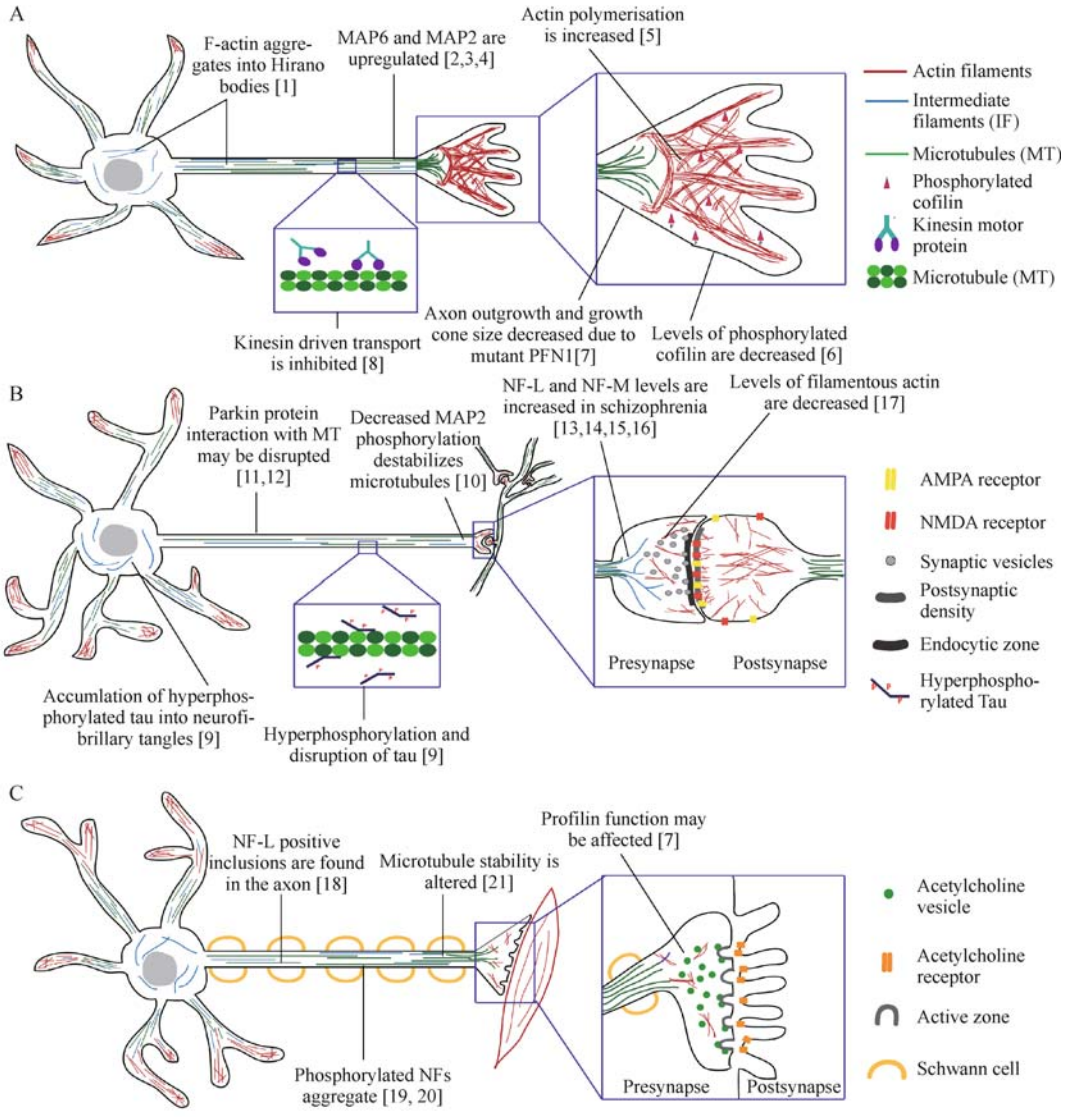

Figure 1 Cellular architectural changes due to disease or after injury in developing neurons (A), mature neurons in the central nervous system (B) and motor neurons (C). Post mortem studies in schizophrenia patients reveal upregulation of microtubule associated protein (MAP) 2 and 6 in the prefrontal cortex (Anderson et al., 1996 [2], Cotter et al., 2000 [3], Shimizu et al., 2006 [4]). Schizophrenia patients are also associated with up regulation of two isoforms of neurofilaments (NFs), NF-L and NF-M, which is suggested to impact on NMDA receptor localisation to the post synaptic density (Clinton et al., 2003[13], Clinton et al., 2004[14], Ehlers et al., 1995[15], Ehlers et al., 1998[16]). Reductions in phosphorylated cofilin and filamentous actin are shown in dendritic spines in mouse models of schizophrenia (Asrar et al., 2009[17]). Epileptic patients have reduced levels of phosphorylated MAP2 associated with decreased cytoskeletal stability (Sanchez et al., 2001[10]). Increase activation of cofilin, and subsequent reduction in actin stabilisation is observed in epilepsy (Chai et al., 2009[6]). Mutations in the Parkinson's disease associated protein alpha-synuclein, have been associated with increases in the rate of actin polymerisation (Sousa et al., 2009[5]). Accumulation of filamentous actin and actin-associated proteins into rod shaped inclusions termed Hirano bodies are observed in Alzheimer's disease (Galloway et al., 1987[1]). The MAP tau is known to aggregate into neurofibrillary tangles and neuropil threads within neurons in Alzheimer's disease (Goedert et al., 1988[9]). The accumulation of tau also inhibits kinesin-driven anterograde transport, impacting on neurodegeneration (Dixit et al., 2008[8]). Mutations in the parkin protein, which is known to bind microtubules, have been linked to autosomal recessive and sporadic forms of Parkinson's disease (Lucking et al., 2000 [11], Scott et al., 2001 [12]). Mutations in the actin associated protein PFN1 have been identified in familial amyotrophic lateral sclerosis (ALS), with cell culture studies indicating that mutant PFN1 causes decreased bound actin levels, axon outgrowth and growth cone size (Wu et al., 2012[7]). Mouse models of ALS show NF-L only inclusions in the spinal cord of pre-symptomatic mice (Morrison et al., 2000[18]). ALS patients also exhibit aggregation of phosphorylated NFs in the perikarya and proximal axons (Manetto et al., 1988[19], Munoz et al., 1988 [20]). Alterations to the normal functioning of NFs in ALS may lead to alterations in microtubule stability due to inhibition of normal NF-MT binding (Bocquet et al., 2009[21]).

pools and impaired synaptic plasticity, similar to the synaptic defects thought to occur in schizophrenia (Andrieux et al., 2002). Subsequent studies have revealed that MAP6 deletion results in both positive and negative symptoms as well as cognitive impairments seen in schizophrenia (Brun et al., 2005; Bégou et al., 2007; Powell et al., 2007; Bégou et al., 2008). Together, this suggests that alterations in the regulation of microtubules may play a role in schizophrenia disease progression.

Epilepsy

Epilepsy is a common neurological disorder characterized by seizures, learning disabilities and memory problems. As epilepsy is primarily a disorder of electrical excitability, it is postulated that abnormalities in dendritic spines are implicated in the etiology of the disease.

The most common, pharmacoresistant, form of epilepsy is temporal lobe epilepsy (TLE). Patients with TLE have been shown to present with a decrease in dendritic spine density in hippocampal pyramidal neurons and dentate granule cells (Scheibel et al., 1974; Belichenko and Dahlström, 1995; Freiman et al., 2011). TLE is commonly characterized by a loss in the compact lamination of granule cells, resulting in granule cell dispersion (Houser, 1990). The extracellular matrix protein Reelin has been shown to be deficient in TLE and directly cause granule cell dispersion (Haas et al., 2002). Reelin has been shown to stabilize the actin cytoskeleton by phosphorylating, and thereby inactivating, cofilin (Chai et al., 2009). This suggests that a loss of Reelin, as seen in TLE, results in reduced phosphorylation and therefore increased activation of cofilin, thereby reducing the stability of the actin cytoskeleton and contributing to increased granule cell dispersion. It is likely, that this change in the stability of the actin cytoskeleton has adverse effects on the structure and morphology of dendritic spines, impacting on neuronal transmission in TLE patients.

MAP2 has also been implicated in TLE. Epileptic patients have been shown to have reduced MAP2 phosphorylation in areas of the neocortex displaying spiking activity (Sánchez et al., 2001). The phosphorylation of MAP2 at these specific sites has been associated with decreased microtubule stability due to decreased interaction between MAP2 and microtubules (Sánchez et al., 2000, 2001). MAP2 has been shown to be integral to the stability of neurons, localizing to the dendritic compartment in mature neurons (Caceres et al., 1984) and promoting microtubule assembly (Matus, 1988). Reduced MAP2 phosphorylation is thought to be a consequence of seizure activity (Díez-Guerra and Avila, 1993; Sánchez et al., 2001), with decreased levels of phosphorylated MAP2 subsequently impacting on the stability of the cytoskeleton and potentially leading to neuronal damage and loss (Sánchez et al., 2001). Therefore, cytoskeletal changes to both the microtubule and actin filament networks in epilepsy result due to decreased stability of filament systems. Instability of the cytoskeleton has downstream effects on neuronal transmission and connectivity.

Neurodegenerative disorders

Alzheimer's disease

The term neurodegeneration refers to the progressive loss of neuronal structure and/or function. Although this process is a physiologically normal event that occurs during aging, numerous diseases are characterized by premature neuronal death. Diseases such as AD and PD are incurable diseases that are associated with protein assemblies, increased cell death and disruption to the neuronal cytoskeleton.

AD is the most common form of dementia, with over 5 million new cases reported annually. Its incidence increases from 1% between the ages of 60 and 70, to around 7% in people over 85 years of age (Ferri et al., 2005). AD is associated with an abnormal decline in cognition, which is related to cytoskeletal changes in neurons and subsequent neurodegeneration. Current treatments provide only mild symptomatic relief without halting or slowing disease progression. Histopathologically, AD is characterized by extracellular deposits of amyloid-β (Aβ) protein, which form plaques within the brain and aggregation of the MAP tau, which forms neurofibrillary tangles (NFTs) and neuropil threads (NT) within neurons (Goedert et al., 1988). Accumulation of NFTs results in a number of disturbances to the neuronal network including loss of synapses, the death of neurons and impairments to the structural and regulatory functions of the neuronal cytoskeleton (Ballatore et al., 2007).

The accumulation of the microtubule binding protein tau has been well characterized in both post-mortem and animal studies of AD (reviewed in (Hanger et al., 2009; Ke et al., 2012). There are several hypotheses on how a loss of normal tau function impacts on microtubules. First, as the normal function of tau is to stabilize microtubules, and hyperphosphorylation of tau reduces its affinity for microtubules and reduces its ability to stabilize microtubules into organized arrays in vitro (Wagner et al., 1996; Patrick et al., 1999), it is believed that microtubules are disassembled in AD due to a loss of normal tau function (Schneider et al., 1999). Secondly, pathological forms of tau may gain toxic functions such as increased incidence of misfolded and fibrillar tau, as well as increased formation of NFTs (Trojanowski and Lee, 2005). Alternatively, the dissociation of tau from microtubules may cause microtubules to degrade as they become more sensitive to microtubule severing proteins such as katanin (Qiang et al., 2006; Sudo and Baas, 2011).

Neuronal transport is affected in AD either through a loss or gain of normal tau function. In AD, it has been shown that the accumulation of tau in the somatodendritic compartment inhibits kinesin-driven anterograde transport, impacting on neurodegeneration (Dixit et al., 2008). Monomeric tau can block the initial attachment of motor proteins to microtubules

and thereby interfere with microtubule-driven transport (Ebneth et al., 1998; Seitz et al., 2002). However, other reports indicate that the interaction between tau and microtubules does not directly affect kinesin or cytoplasmic dynein-based motility (Morfini et al., 2007). Although it is likely that hyperphosphorylation of tau impacts on microtubule dynamics, the exact role of tau *in vivo* in healthy neurons and in disease is still unclear. Importantly, recent work identified a critical role of tau in mediating NMDA receptor-dependent excitotoxicity by targeting the Fyn kinase to the post synapse suggesting an involvement of tau in the pathology that is independent on its role in stabilizing microtubules and that inhibition of tau function may have a protective effect (Ittner et al., 2010). Therefore, although microtubules may not be directly implicated in the initiation of the disease, both a gain and loss of normal tau function has drastic implications on the normal functioning of the neuronal cytoskeleton in AD.

Although the majority of research into AD focuses on the microtubule cytoskeleton, actin filaments have also been shown to be involved in AD pathology. Tau induced neurodegeneration has been associated with the accumulation of F-actin and actin-rich rods in animal models expressing mutant tau (Fulga et al., 2007). These rods are caused by the excessive dephosphorylation of cofilin, which saturates actin filaments causing their aggregation and accumulation in neurites (Nishida et al., 1987; Minamide et al., 2000). Therefore, the accumulation of these rods could impact on normal synaptic function as they potentially inhibit intracellular transport at the synapse (Minamide et al., 2000). Hirano bodies are a separate type of rod shaped inclusion in AD that consist mainly of F-actin and actin binding proteins (Galloway et al., 1987). They are predominantly found in neuronal processes in the CA1 region of the hippocampus. Their incidence increases with advanced age in normal individuals and is particularly prominent in AD patients (Gibson and Tomlinson, 1977; Schmidt et al., 1989). Several changes in levels of actin binding proteins have been documented in Hirano bodies. First, cofilin, which binds and severs F-actin was shown by immunohistochemical analysis to be a major component of Hirano bodies (Maciver and Harrington, 1995). Immunostaining of Hirano bodies also revealed the presence of fractin, a caspase cleaved actin fragment, suggesting the alteration of the actin microfilament network by caspases (Rossiter et al., 2000). Although there is no link between rods in neurites and Hirano bodies, it is suggested that rods may be precursors for Hirano bodies as both inclusions consist of ADF/cofilin and actin inclusions (Minamide et al., 2000). Despite clear evidence of the involvement of the actin cytoskeleton in AD, actin is still a less characterized hallmark of AD that needs more attention. As there is clear evidence that the microtubule and actin filament cytoskeletons interact (Dent and Kalil, 2001; Fulga et al., 2007), it is plausible that these filament systems are abnormally interacting in AD, impacting on the progression of the disease.

Parkinson's disease

PD is a progressive neurodegenerative disease associated with motor deficits, which manifest as tremors, rigidity, bradykinesia and gait impairment. Degeneration of dopaminergic neurons in the substantia nigra, pars compacta along with intracellular protein accumulation termed Lewy bodies (LB) are common histopathalogical findings in PD. LB are primarily composed of α-synuclein, however they have also been shown to contain tubulin, MAPs and NFs (Galloway et al., 1992) suggesting the involvement of multiple components of the cytoskeleton. Wild type α-synuclein has been shown to bind to actin and slow its polymerisation. By contrast, the A30P α-synuclein mutant, which is associated with familial PD, increases the rate of actin polymerisation and disrupts the reassembly of the actin cytoskeleton (Sousa et al., 2009). Therefore, the deregulation of α-synuclein in PD may not only lead to accumulation of LBs but also impact on the normal functioning of the neuronal cytoskeleton. The aggregation of NFs in LBs has led to numerous screens of NF mutations in PD. Mutations in the NF-M gene have been identified in patients with PD (Lavedan et al., 2002; Krüger et al., 2003), suggesting that changes to the normal function of NF-M in PD.

The protein parkin has been shown to bind microtubules (Ren et al., 2003) through three independent domains (Yang et al., 2005). Numerous mutations in the parkin gene have been linked to autosomal recessive and sporadic PD (Lücking et al., 2000; Scott et al., 2001). The neurons that degenerate in PD are termed nigral dopaminergic neurons and project to striatal target areas. They have long axons, which rely on microtubule transport to move dopaminergic vesicles over long distances. Therefore, the link between PD and parkin is of particular interest as mutations in parkin may contribute to disruptions in axonal transport in PD. In particular, parkin has been shown to supress microtubule depolymerisation and may therefore protect midbrain dopaminergic neurons against microtubule depolymerisation (Ren et al., 2009), a process that may be lost in PD.

Amyotrophic lateral sclerosis

ALS, also called Lou Gehrig's disease, is a progressive motor neuron disease resulting in neuron death and subsequent muscle dysfunction. About 90% of ALS cases are sporadic (sALS), while the remaining 10% are familial (fALS), inherited in a dominant manner. ALS is characterized by dysfunctional RNA processing, endoplasmic reticulum stress, mitochondrial dysfunction, excitotoxicity, proteosomal dysfunction, impaired axonal transport and protein aggregation (Bento-Abreu et al., 2010). Transgenic mouse models (Collard et al., 1995) and histopathological studies (Munoz et al., 1988) implicate cytoskeletal proteins in the neurodegeneration of ALS.

The aggregation of phosphorylated NFs in the perikarya and proximal axons, which are normally only present in distal

axons and nerve terminals (Sternberger and Sternberger, 1983), are a common pathological finding in both fALS and sALS (Manetto et al., 1988; Munoz et al., 1988). This indicates abnormal phosphorylation and transport of NFs in the diseased state. Furthermore, the use of transgenic mice, which overexpress IF proteins, has revealed alterations in the stoichiometry of NF subunit protein expression levels in ALS (Côté et al., 1993; Xu et al., 1993; Lee et al., 1994).

Although variations in the NF-H gene have been shown to account for only 1% of sALS (Figlewicz et al., 1994; Al-Chalabi et al., 1999), overexpression of human NF-H in mice causes a progressive neuropathy with impaired NF transport resulting in neuronal swelling and axonopathy, similar to the pathology observed in ALS (Côté et al., 1993). Transgenic mice that accumulate approximately 4-times the normal level of NF-L have similar NF accumulations to those found in ALS. These mice also show increased axonal degeneration and motor dysfunction, but without extensive motor neuron death (Xu et al., 1993). A decrease of 70% in NFL mRNA levels has been reported in degenerating neurons in ALS (Bergeron et al., 1994; Wong et al., 2000). Furthermore, the ALS-linked SOD1 mutant protein binds to and destabilizes NFL mRNA, a property which is not observed in normal SOD1 proteins (Ge et al., 2005). In SOD-1 mutant mice NF-L only containing inclusions are present in the spinal cord of pre-symptomatic mice (Morrison et al., 2000). Furthermore, high NF-L and NF-H levels and autoantibodies against NF-L have been documented in cerebrospinal fluid in ALS patients (Brettschneider et al., 2006; Niebroj-Dobosz et al., 2006; Tortelli et al., 2012). The measurement of CSF NF-L levels was found to have a sensitivity of 78.4% and a selectivity of 72.5% (Tortelli et al., 2012), with suggestions that NF-L could be used as a biomarker for ALS.

NFs regulate the number of MTs in the axon via their microtubule polymerisation inhibitory domain (Bocquet et al., 2009) and also have binding sites for myosin Va motor proteins (Rao et al., 2011). Therefore, a disruption to the IF system would likely impact on the regulation of levels and localization of organelles within the axoplasm, further contributing to the diseased state.

Recently, exome sequencing of two different ALS families identified mutations in the profilin 1 gene (*PFN1*), with the mutations shown to lie in close proximity to actin binding residues (Wu et al., 2012). Cells expressing PFN1 mutants displayed decreased binding to actin, a significant decrease in axon outgrowth and growth cone size relative to wild-type PFN1 expressing cells. Mutant PFN1 was also shown to form insoluble aggregates, which was not seen in wild-type PFN1. Furthermore, 30%–40% of primary motor neurons containing cytoplasmic PFN1 aggregates tested positive for the ALS-related protein TDP-43. PFN1 mutation carriers have been shown to typically present with a spinal onset ALS phenotype (Wu et al., 2012; Ingre et al., 2013). Taken together, this suggests a role for mutant *PFN1* in inhibiting axon dynamics and contributing to fALS pathology, which has already been shown to occur in mutant SOD1 (Takeuchi et al., 2002) and TDP-43 (Duan et al., 2011) proteins.

However, although several mutations in *PFN1* have been identified (Wu et al., 2012; Chen et al., 2013; Ingre et al., 2013; Tiloca et al., 2013; van Blitterswijk et al., 2013) most subsequent studies indicate limited prevalence of mutant PFN1 in ALS. Although it was initially thought that mutant *PFN1* is likely to only account for 1%–2% of fALS cases, the somewhat negative results of subsequent studies (Chen et al., 2013; Daoud et al., 2013; Lattante et al., 2013; van Blitterswijk et al., 2013; Yang et al., 2013; Zou et al., 2013) suggest it is likely that larger sample sizes are needed to verify the true prevalence of PFN1 mutations in ALS.

Therapeutic intervention

The large body of evidence for the involvement of the cytoskeleton in neurodegenerative diseases, motor function deficits and mental disorders warrants research into drugs, which stabilize the cytoskeleton and thereby limit disease progression.

Historically, epilepsy has been treated by targeting neurotransmitter receptors and ion channels. As seizures cause injury to the actin cytoskeleton, studies are currently underway to stabilize the actin cytoskeleton and therefore spine morphology in epilepsy (Zeng et al., 2007). Calcineurin is a calcium-dependant phosphatase. Calcineurin inhibitors, such as FK506, have been shown to limit seizure-induced dendritic injury (Zeng et al., 2007). Although FK506 does not reduce kainite seizure latency or severity, it has been shown to prevent neuronal death after seizures, decrease excitatory postsynaptic potentials and enhance LTP (Moriwaki et al., 1998). Therefore, FK506 has been suggested to have protective effects against mechanisms of seizure-induced dendritic injury via direct calcineurin-mediated modulation of actin (Zeng et al., 2007).

As previously discussed, the microtubule network is disrupted in AD. Taxol, a drug traditionally used for cancer treatment, is a well-known microtubule stabilizing drug and was therefore suggested as a therapeutic substitute for tau. In mouse models of AD, intravenous administration of taxol resulted in improved axonal transport in spinal axons accompanied by an increase in microtubule numbers (Zhang et al., 2005). However, there is still considerable debate on the benefit of taxol as numerous studies have revealed that even low doses of taxol can produce painful and often debilitating peripheral neuoropathies (Baas and Ahmad, 2013). Furthermore taxol does not cross the blood brain barrier and therefore its practicality in treating neurological disorders is questionable. The microtubule stabilizing drug epothilone D (EpoD), has since been shown to cross the blood brain barrier as well as improve cognitive performance in tau transgenic mice (Brunden et al., 2010). Furthermore, in aged mice with tau pathology and related behavioral deficits,

Table 1 Diseases involving the cytoskeleton

Disorder	Lead symptoms	Filament system affected	Reference
Alzheimer's disease	Dementia	MT, AF	Grundke-Iqbal et al., 1986a; Grundke-Iqbal et al., 1986b; Iqbal et al., 1986; Maciver and Harrington, 1995; Li et al., 2007
Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)	Behavioral deficits Parkinsonism	MT	Hutton et al., 1998; Rovelet-Lecrux and Campion, 2012
Parkinson's disease	Bradykinesia Muscle rigidity Resting Tremor Postural instability	IF, MT	Hill et al., 1991; Yang et al., 2005; Ren et al., 2009
Amyotrophic lateral sclerosis	Muscle dystrophy	IF, AF	Sternberger and Sternberger, 1983; Tortelli et al., 2012
Charcot-Marie-Tooth disease	Muscle dystrophy	IF	Yoshihara et al., 2002; Jordanova et al., 2003; Pérez-Ollé et al., 2005
Huntington's disease	Dementia Disordered movement	IF, MT	Dom et al., 1976; DiProspero et al., 2004
Epilepsy	Seizures	AF	Scheibel et al., 1974; Ouyang et al., 2007
Schizophrenia	Chronic psychosis Cognitive impairment	AF	Glantz and Lewis, 2000, 2001; Rubio et al., 2012
Giant axonal neuropathy	Reduced strength Reduced reflexes	IF, MT	Asbury et al., 1972; Prineas et al., 1976; Mahammad et al., 2013
Spinal muscular atrophy	Areflexia Spinal cord and muscle atrophy	AF, IF	Rossoll et al., 2003; Torres-Benito et al., 2012

MT = microtubules; AF = actin filaments; IF = intermediate filaments.

administration of EpoD reduced axonal dystrophy, increased axonal MT density and subsequent improvement in fast axonal transport and cognitive performance (Zhang et al., 2012). The ability of EpoD to improve axonal defects after the neurodegenerative process has begun gives great promise to the drug as a potential treatment of AD and other tauopathies.

The cause of neurological disorders is still largely unknown and this limits the design of effective treatments. Increasing evidence supports the involvement of different components of the cytoskeleton in disease, either through initiation or progression of pathology. Therefore, research into targeting the neuronal cytoskeleton is of great significance. As numerous filament systems (see Table 1.) are disrupted in these diseases, a systematic approach, targeting multiple filament systems, may be a more effective means to treat these neurological disorders.

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Compliance with ethic guidelines

Alexandra K. Suchowerska and Thomas Fath declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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