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Multiple roles for the cytoskeleton in ALS

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease caused by more than sixty genes identified through classic linkage analysis and new sequencing methods. Yet no clear mechanism of onset, cure, or effective treatment is known. Popular discourse classifies the proteins encoded from ALS-related genes into four disrupted processes: proteostasis, mitochondrial function and ROS, nucleic acid regulation, and cytoskeletal dynamics. Surprisingly, the mechanisms detailing the contribution of the neuronal cytoskeletal in ALS are the least explored, despite involvement in these cell processes. Eight genes directly regulate properties of cytoskeleton function and are essential for the health and survival of motor neurons, including: *TUBA4A*, *SPAST KIF5A*, *DCTN1*, *NF*, *PRPH*, *ALS2*, and *PFN1*. Here we review the properties and studies exploring the contribution of each of these genes to ALS.

Keywords

Microtubules; Actin; Cytoskeleton; Amyotrophic lateral sclerosis (ALS)

1. Introduction: the cytoskeleton is a convergence point in ALS

Amyotrophic lateral sclerosis (ALS) is a rare and fatal disease (Lasiene and Yamanaka, 2011; Phatnani et al., 2013; Ragagnin et al., 2019). Although close to 95% of all ALS cases are sporadic, genetic studies have identified that mutations in *SOD1*, *C9ORF72*, *FUS*, and *TDP43* genes may account for ~60% of all inherited cases, albeit with large variations in the disease penetrance and severity (Renton et al., 2014; Gregory et al., 2020; Masrori and Van Damme, 2020; Nguyen et al., 2018). ALS pathogenesis is characterized by the degeneration of motor neurons and disturbances to glia that further impair mechanisms of glia-motor neuron interaction and trophic support (Philips and Rothstein, 2014). Many different

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mechanisms are thought to explain disease onset including impairments to proteostasis, DNA repair, RNA metabolism, neuronal excitability, and intracellular transport. Notably, the neuronal cytoskeleton (e.g., actin filaments, intermediate filaments, and microtubules) is a convergence point required to execute each of these functions, and is clearly disrupted in mammalian cell models recapitulating ALS. *SOD1* mutations gain affinity for actin and tubulin, which impairs neuronal growth cones and mitochondria fission (Osking et al., 2019; Muñoz-Lasso et al., 2020). *C9orf72* acts as a roadblock to kinesin and dynein motor-based transport, and also disrupts actin filament disassembly (Fumagalli et al., 2021; Shiota et al., 2022; Webster et al., 2018; Sivadasan et al., 2016). Cytoplasmic inclusions of FUS prevent ribonucleotide cargos from reaching their normal locations by aberrantly sequestering motor proteins and influencing the post-translational states of microtubule tracks (Yasuda et al., 2017). Finally, the presence of pathological TDP-43 in the cytoplasm of motor neurons is correlated with diminished axon length, complexity, and mitochondrial transport (Herzog et al., 2017; Oberstadt et al., 2018a; Briese et al., 2020).

Disease-induced disturbances to axonal transport may be the most obvious connection between ALS and the cytoskeleton, because it conveniently explains several disparate phenotypes including: the aberrant localization of diverse proteins, lipids, and organelles; the accumulation of misfolded proteins or toxic aggregates from reduced clearance; and the decreased transmission of neuronal signals (Julien and Beaulieu, 2000; Castellanos-Montiel et al., 2020; Theunissen et al., 2021; Millecamps and Julien, 2013). All these scenarios may arise through deficits in functional tracks, motor proteins, cargo, or the adapter proteins used to connect cargos to the motors walking on the tracks (Fig. 1A) (Kapitein and Hoogenraad, 2015; Coles and Bradke, 2015; Tas et al., 2017; Saxton and Hollenbeck, 2012; Leterrier, 2021; Hammer and Wagner, 2013; Chua et al., 2012; Lewis et al., 2009). Normally, neuronal cargos are transported far distances (>1 m) along microtubules and move at different speeds and directions depending on the cargo and the linking motor (Nirschl et al., 2017). For perspective, the fastest kinesin motors take >4 days to traverse microtubules spanning the length of the longest motor neurons! To reach their final destinations, some ALS-relevant cargos are transferred from microtubules to actin filament tracks (Fig. 1B) (Coles and Bradke, 2015; Nirschl et al., 2017; Ally et al., 2009; Dogterom and Koenderink, 2019; Pimm and Henty-Ridilla, 2021). Microtubule or actin filament highways that become dilapidated, disassembled, or otherwise unpassable prevent neurons from transmitting cellular distress signals or receiving essential maintenance factors. Thus, even small impediments to or accumulated inefficiencies in this system explain an important component of symptomatic onset.

Although more than sixty ALS-causative genes have been identified, only eight encode key cytoskeletal proteins, including: α-tubulin (TUBA4A), spastin (SPAST), kinesin (KIF5A), a subunit of the dynein-dynactin complex (DCTN1), neurofilament (NF), peripherin (PRPH), alsin (ALS2), and profilin (PFN1) (Cirulli et al., 2015; Wu et al., 2012; Liu et al., 2017; Smith et al., 2014; Zhang et al., 2019). Each is linked to transport mechanisms, is required for normal development, is present in cells besides those affected by ALS, and with the exception of ALS2, is inherited in a dominant manner (Table 1) (Millecamps and Julien, 2013; Yang et al., 2001; Topp et al., 2005). Pathogenic variants of these genes only explain <5% of all ALS cases (Table 1) (Cirulli et al., 2015; Wu et al., 2012; Liu et al., 2017;

Smith et al., 2014; Zhang et al., 2019), and disruptions to intracellular transport alone do not completely explain the nuance of disease onset. The timing of ALS onset remains a major open question, as most patients do not present noticeable symptoms until middle age, when numerous cell activities fail. Changes in the expression of some cytoskeleton-related genes coincide with symptomatic onset, including an increase in intermediate filament proteins (e.g., NF and PRPH) and the reduced expression of tubulin, syntaxin1B, dynactin subunits, and glutamate receptors (Julien et al., 1995; Robertson et al., 2003; Poesen and Van Damme, 2019; Zucchi et al., 2020; Wang et al., 2021; Yadav et al., 2022). Nevertheless, such studies assessing the contribution of cytoskeleton-related genes to ALS onset are further compounded by the absence of these genes from available expression surveys (Yadav et al., 2022; Jiang et al., 2005). Here we discuss the contribution of cytoskeleton genes in ALS including and beyond functions as an intracellular shipping system. Understanding these mechanisms may offer insight into neuronal function and additional considerations for emerging therapies.

2. Microtubule highways: main tracks for transport

Intracellular trafficking defects are linked to nearly all forms of ALS, regardless of gene variant (Castellanos-Montiel et al., 2020; Burk and Pasterkamp, 2019). Are these disruptions a cause or are they caused indirectly through the cacophony of other dysfunctional cell functions impinging on the cytoskeleton? Neuronal transport requires a specific arrangement of actin filaments and microtubules for normal function (Fig. 1). Although not perfectly uniform, most neuronal microtubules are oriented with growing plus-ends toward terminal actin-rich growth cones, and stable minus-ends pointing toward the cell body (Fig. 1A) (Coles and Bradke, 2015; Tas et al., 2017; Leterrier, 2021).This arrangement effectively allows plus-end directed kinesin motors to move cargos toward the cell periphery (e.g., anterograde transport) and minus-end directed dynein motors to shuttle cargos inward toward the cell body (e.g., retrograde transport) (Fig. 1A). Intermediate filaments reinforce actin and microtubule paths but do not serve as tracks for transport (Bott and Winckler, 2020). No direct evidence (i.e., ALS-causative mutations in actin or myosin motors) suggests actin filament tracks are compromised or defective in ALS (Sundaramoorthy et al., 2015). Thus, transport relevant to ALS is predominately microtubule-based (Fig. 1B). Whether disease mutations build compromised tracks or alter microtubule dynamics remains an important open question.

There are multiple isoforms of tubulin, and each assemble into microtubules in a concentration-dependent process where tubulin dimers build protofilaments from templates (e.g., γ-TuRc) to form microtubule tracks (Fig. 3A) (Kapitein and Hoogenraad, 2015; Buscaglia et al., 2020). 1.4% of ALS cases are explained by nine autosomal dominant mutations present in a single isotype of tubulin, TUBA4A (V7I, G43V, T145P, R215C, R320C, R320H, A383T, W407X, and D438N) (Table 1; Fig. 2A) (Smith et al., 2014; Pensato et al., 2015; Van Damme et al., 2017). TUBA4A is present but not the most abundant α-tubulin in neurons, and becomes down-regulated before disease onset (Yadav et al., 2022; Jiang et al., 2005; Buscaglia et al., 2020). Whether TUBA4A mutations compromise the overall structure or motor protein functions is not clear. At least two ALS-related residues are located adjacent to the β-tubulin binding surface (T145 and W407)

(Fig. 2A). These mutations may limit the association of β-tubulin and disrupt heterodimer formation (Fig. 3A). Further, while no ALS-related residues appear on the surface that mediates interactions with motor proteins, disruptions to protofilament assembly could alter the binding or movement of microtubule motors. Testing these ideas directly will require specific systems that use only the TUBA4A isotype (Davis et al., 1993; Sackett et al., 2010; Ti et al., 2020). However, experiments from COS7 cells overexpressing TUBA4A (W407X) suggest that both microtubule tracks and polymerization are compromised (Fig. 3B) (Smith et al., 2014).

In addition to mechanisms involving tubulin alone, hundreds of other proteins regulate the dynamics of neuronal microtubules. For example, SPAST disassembles microtubules by pulling on the C-terminal tail of α- and β-tubulin dimers to excise individual tubulin subunits from the microtubule lattice (Vemu et al., 2017; Sandate et al., 2019; Han et al., 2020). This mechanism generates pieces of microtubules that may serve as templates for new microtubule assembly (Roll-Mecak and Vale, 2008; Wood et al., 2006), or contribute to the loss of functions seen with the TUBA4A(W407X) nonsense mutation that lacks the α-tubulin tail (above). While SPAST is the primary cause of hereditary spastic paraplegia (HSP), three unrelated mutations (S44L, R65H, and N542G) also cause ALS (Table 1; Fig. 2B) (Cirulli et al., 2015; Münch et al., 2008; Meyer et al., 2005; Brugman et al., 2009; Tremolizzo et al., 2014). These mutations eliminate SPAST's microtubule binding and disassembly activities, leading to undesirable microtubule growth (Fig. 3B). Furthermore, the loss of functional SPAST increases microtubule polyglutamylation, which in turn reduces the microtubule affinity of kinesin motors (particularly KIF5), and suppresses overall anterograde transport (Lopes et al., 2020; Solowska et al., 2008). In contrast to SPAST, PFN1 stimulates assembly by binding tubulin dimers and microtubules (Henty-Ridilla et al., 2017; Pimm et al., 2022). Some variants eliminate these functions and redistribute cellular PFN1 pools, disrupting the delicate coordination of microtubules and actin filaments at transport terminals, discussed further below (Henty-Ridilla et al., 2017; Pinto-Costa et al., 2020). Thus, compromised structural integrity of microtubule tracks through mutations in tubulin building blocks or essential regulatory proteins have devastating consequences for intracellular transport and overall neuronal health (Liang et al., 2016; Dumont et al., 2015; Kabir et al., 2020; Morikawa et al., 2015; Triclin et al., 2021; Thery and Blanchoin, 2021; Budaitis et al., 2021).

3. Tethering cargos to tracks: motors and cargo-linking proteins

Kinesin-1 motors (e.g., KIF5A) navigate microtubule tracks to mediate the anterograde transport of mitochondria, vesicles, and signaling molecules (Fig. 1) (Hirokawa and Takemura, 2005). KIF5A is exclusively expressed in motor neurons, essential for development and function, and the only kinesin with reported mutations that cause ALS (Nicolas et al., 2018; Niclas et al., 1994; Fagerberg et al., 2014; Brenner et al., 2018; He et al., 2020; Baron et al., 2022). The twelve variants (0.2% prevalence) linked to ALS or the Δ544–1032 truncation, localize to several conserved functional domains including: the motor (K29R, P46S, S291G, and R297Q), the coiled-coil (E413G, Q474G, H542N, and G577S), and a C-terminal cargo binding region (P986L, T1001Q, R1007K, and Δ544–1032) (Table 1; Fig. 2C) (Zhang et al., 2019; Nicolas et al., 2018). Regardless of variant, the

mechanism of impaired long-range cargo transport is most likely failed motor locomotion or aberrant cargo unions that either unlink normal ligands or load new disease-relevant ones onto tracks. In zebrafish or rat hippocampal neurons the reduction of KIF5A results in hyperexcitability, axonal degradation, and defective mitochondrial transport that cannot be restored with other KIF5 isoforms or kinesin motors (Campbell et al., 2014; Zhao et al., 2020; Xia et al., 2003). Overexpression of a disease relevant fragment of KIF5A's cargo binding domain releases autoinhibition and hyper-activates axonal transport and aberrant interactions with RNA (Baron et al., 2022). In contrast, modulating KIF5A had no observable effect on anterograde transport in SOD1 disease models (Shi et al., 2010), implying that additional motors interact or interfere with neuronal cargos in ALS.

In contrast to kinesin, dynein motors cruise along microtubules and require the dynactin complex as a cofactor to execute retrograde transport (Fig. 1) (Schroer, 2004). Twelve ALS-relevant mutations manifest in only DCTN1, which directly links cargos to the motor and improves dynein's processivity (E34Q, G59S, D63Y, M571T, R785W, R1101K, and T1249I) (Table 1; Fig. 2D) (Nicolas et al., 2018; Lau et al., 2021; Waterman-Storer et al., 1995; Vaughan et al., 2002; Holzbaur and Vallee, 1994; Puls et al., 2003). ALS-related disruptions through DCTN1 (G59S) prevent the linkage of essential cargo to dynein-based transport systems, which in turn impairs motor neuron development and synaptic function (Liu et al., 2017; Bercier et al., 2019; Kuźma-Kozakiewicz et al., 2013; Levy et al., 2006; Moore et al., 2009; Lai et al., 2007). DCTN1 is the only cytoskeleton-related gene associated with polygenic manifestations of ALS, found in combination with variants of dynein-transported cargos, specifically SETX, ATXN2, FIG. 4, and C9ORF72 (Cady et al., 2015). Further, even without DCTN1 variants, all observed polygenic ALS cases display disease-related impairments to retrograde transport (Shi et al., 2010; Kuźma-Kozakiewicz et al., 2013; Maimon et al., 2021). Many mechanisms may explain the transport defects for these commonly misfolded proteins including that dynein-linkage sights become obscured (Cristofani et al., 2017; Licata et al., 2022). Regardless of the exact mechanism detailing the engagement between microtubules, motors, or cargos, defects in axonal transport are an established feature of ALS and other neurodegenerative diseases.

4. Intermediate filament aggregation is a pathological hallmark of ALS

Intermediate filaments (e.g., NF and PRPH) are formed from a dynamic self-assembly process, but unlike actin or microtubules the final polymers lack polarity and do not act as tracks for intracellular transport (Fig. 3C) (Xiao et al., 2006; Yuan et al., 2017). Instead, NF and PRPH influence transport on actin and microtubules by structurally reinforcing those filaments (Xiao et al., 2006; Yuan et al., 2017). Aggregates of either NF or PRPH intermediate filament proteins are a considered early pathological hallmarks of ALS, and found in nearly all patients, directly causing 0.22% of all familial ALS (Table 1) (Cirulli et al., 2015; Gros-Louis et al., 2004; Leung et al., 2006; Corrado et al., 2011; Corbo and Hays, 1992). However, the metaphorical road to pathological onset through intermediate filaments is bumpy and confusing. Disease-relevant hyperphosphorylation of NF and PRPH is thought to occur before noticeable defects in axonal transport because motor neurons in disease models often degenerate before aggregates form; this could trigger intermediate filament aggregation and also slowed transport (Fig. 3D) (Robertson et al., 2003; Beaulieu

et al., 2000). However, this model does not consider whether pathological inclusions are present but below the detection readouts used to visualize aggregate formation, or changes to axonal transport, how NF and PRPH copolymers may contribute to pathological onset, or models that suggest intermediate filament compilations act as protective agents against the disease (Corbo and Hays, 1992; Hirano, 1991; Ho et al., 1998; Julien and Mushynski, 1998; Beaulieu and Julien, 2003). Unfortunately, neither NF or PRPH can be produced in conventional purification and expression systems for use in biochemical assays that to directly address some of these ideas or further decipher the mechanisms of intermediate filament quality control (Bott and Winckler, 2020; Didonna and Opal, 2019).

5. ALS2 and PFN1: direct links to disease-related actin dynamics?

Actin filament regulation is essential for all cells, but particularly critical for neurons, regulating neuronal outgrowth, organelle biogenesis, the stability of axons, and synaptic function (Coles and Bradke, 2015; Leterrier, 2021; Konietzny et al., 2017; Venkatesh et al., 2020). Similar to microtubules, the spontaneous ordered assembly of actin filaments, is concentration-dependent and imparts structural polarity to polymers important for mechanisms of intracellular transport and force generation (Fig. 3E) (Pollard, 2016). ALS2 and PFN1 are almost exclusively studied in the context of actin polymerization in ALS, because direct links to actin dynamics to ALS have been difficult to isolate from other critical cell processes, and because both are also linked to neuronal microtubules and other important regulatory processes.

ALS2 regulates actin-based neurite outgrowth as a prominent guanine nucleotide exchange factor (GEF) for the small GTPase Rab5 (Yang et al., 2001; Topp et al., 2005; Hadano et al., 2001; Cai and Yang, 2016; Tudor et al., 2005; Devon et al., 2006). Together these proteins regulate actin polymerization associated with early endosome dynamics. ALS2 mutations (A261A and K1548G) and deletions produce a very rare (0.007%), autosomal recessive form of juvenile ALS (Table 1; Fig. 2E) (Cirulli et al., 2015; Hamida et al., 1990; Hentati et al., 1994; Alsultan et al., 2016). The pathomechanism of these mutations likely involves unlinking or disturbing the connections between ALS2 and Rab5, which reduces actin-based intracellular trafficking and glutamate signaling at synapses (Lai et al., 2009). However, ALS2 colocalizes at sites of actin and microtubule overlap and is also capable of phase-separation mediated through a region containing A261, but we do not know if these observations are relevant to ALS (Topp et al., 2005; Tudor et al., 2005; Gautam et al., 2016; Sato et al., 2018; Kunita et al., 2007; Millecamps et al., 2005; Hsu et al., 2018). Indeed, neurons devoid of ALS2 display a significant increase in glutamate receptors, autophagy, and sensitivity to oxidative stress, which are each regulated by actin filament assembly and other mechanisms (Fig. 3F) (Gautam et al., 2016; Cai, 2005; Millecamps et al., 2010).

PFN1 variants (A20T, C71G, T109M, M114T, E117G, G118V, R136W, and Q139L) cause an autosomal dominant form of ALS that disturbs actin dynamics in two opposing ways (Table 1; Fig. 2F) (Wu et al., 2012; Alsultan et al., 2016; Ingre et al., 2013; Tiloca et al., 2013; Boopathy et al., 2015). First, PFN1 directly binds to actin monomers, preventing actin filament assembly by blocking the site of new monomer addition (Fig. 3E and F) (Boopathy et al., 2015; Skruber et al., 2018; Pimm et al., 2020; Davey and Moens, 2020;

Suarez and Kovar, 2016; Liu et al., 2022; Ferron et al., 2007). Second, PFN1 enhances actin assembly through interactions with formin proteins (Fig. 3E and F) (Suarez and Kovar, 2016; Liu et al., 2022; Giampetruzzi et al., 2019; Schmidt et al., 2021; Skruber et al., 2019). Combined these properties could directly regulate the shape and function of neuronal growth cones and synapses (Pinto-Costa et al., 2020; Witke et al., 1998; Michaelsen-Preusse et al., 2016; Grintsevich et al., 2021). However, other roles beyond actin regulation also deserve consideration. The interaction between PFN1 and components of the dynactin complex are synthetic lethal in yeast (Figley et al., 2014). PFN1 also potently stimulates microtubule assembly mediated through ALS-relevant mutations, specifically M114T, E117G, and G118V (Henty-Ridilla et al., 2017; Pinto-Costa et al., 2020; Liu et al., 2022). Some PFN1 variants localize to microtubules in cells (Witke et al., 1998; Michaelsen-Preusse et al., 2016). Combined these observations strongly suggest that PFN1 contributes to ALS by regulating the microtubule tracks and transport machinery (e.g. kinesins, dynein, or spastin) (Pimm et al., 2022; Pinto-Costa et al., 2020; Liu et al., 2022; Figley et al., 2014). PFN1 also directly associates with aggregation prone variants of TDP-43, FUS, and UBQLN2 (Rutherford et al., 2013; Kawaguchi et al., 2020; Oberstadt et al., 2018b; Tanaka and Hasegawa, 2016; Matsukawa et al., 2016) and may be related to a protein misfolding or sequestration mechanism that prohibits normal cytoskeletal dynamics or autophagy related processes (Fig. 3F) (Boopathy et al., 2015; Liu et al., 2022; Schmidt et al., 2021; Del Poggetto et al., 2016; Kiaei et al., 2018; Lee et al., 2010). Therefore, additional studies are required to truly decipher whether the cytoskeleton is disrupted due to the presence of cytotoxic aggregates or vice versa.

6. Final thoughts and conclusions

The idea that the cytoskeleton's role in ALS pathology sums to disrupted tracks for transport is certainly a logical and attractive notion, reinforced by the discovery of disease-causing mutations in bona fide microtubule-based machinery. Axonal transport is essential for the homoeostasis of neurons facilitating synaptic communications within and between cells, efficiently clearing disease-relevant protein aggregates, and a common convergence point interrelated to many pathological mechanisms that become compromised in neurodegenerative disease. However, these mechanisms alone do not differentiate ALS from other forms of neurodegeneration or other aggregopathies. While it may not fully explain what is happening to patients suffering from the disease, understanding the basic mechanisms that regulate cytoskeletal proteins is integral to developing specific drug targets for the treatment of ALS. Future studies that combine cell and biochemical approaches will help to dissect these complex questions and the secrets of the tracks and machines inside.

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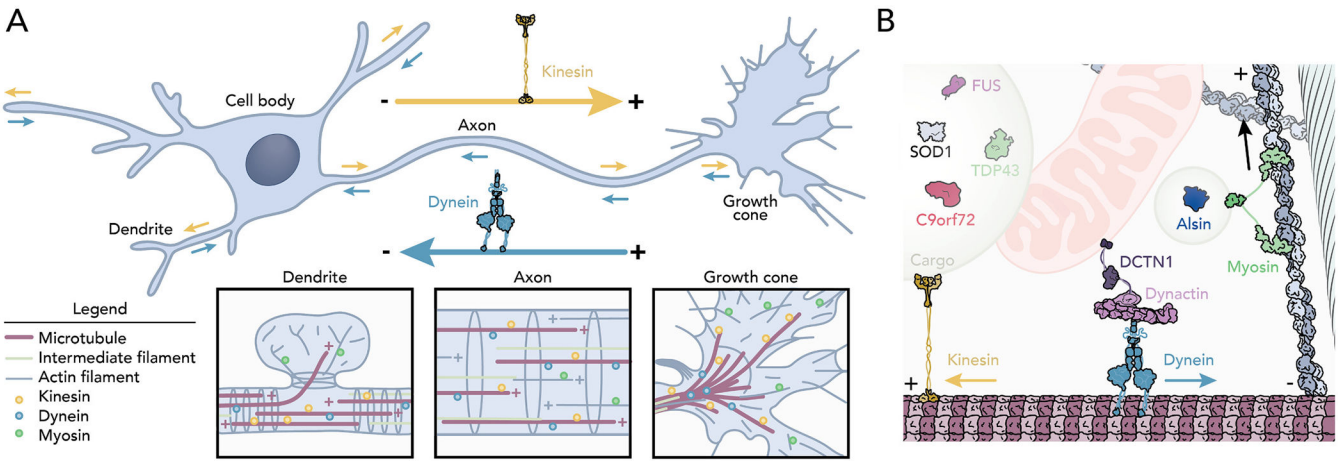

Fig. 1.

The neuronal cytoskeleton as tracks for intracellular transport. (A) Cartoon highlighting the functionally/structurally different features found in motor neurons including: a dendrite, cell body, axon, and growth cone. Kinesin motors (yellow) mediate anterograde transport. Dynein motors (teal) facilitate retrograde transport. Insets: localization of the transport components in (left) dendritic spines, in (middle) the axon, and in (right) growth cones. (B) Cytoskeleton-directed transport. Kinesin, dynein-dynactin complex, and myosin motors move vesicles, mitochondria, intermediate filaments, proteins, and many ALS-related proteins in cells.

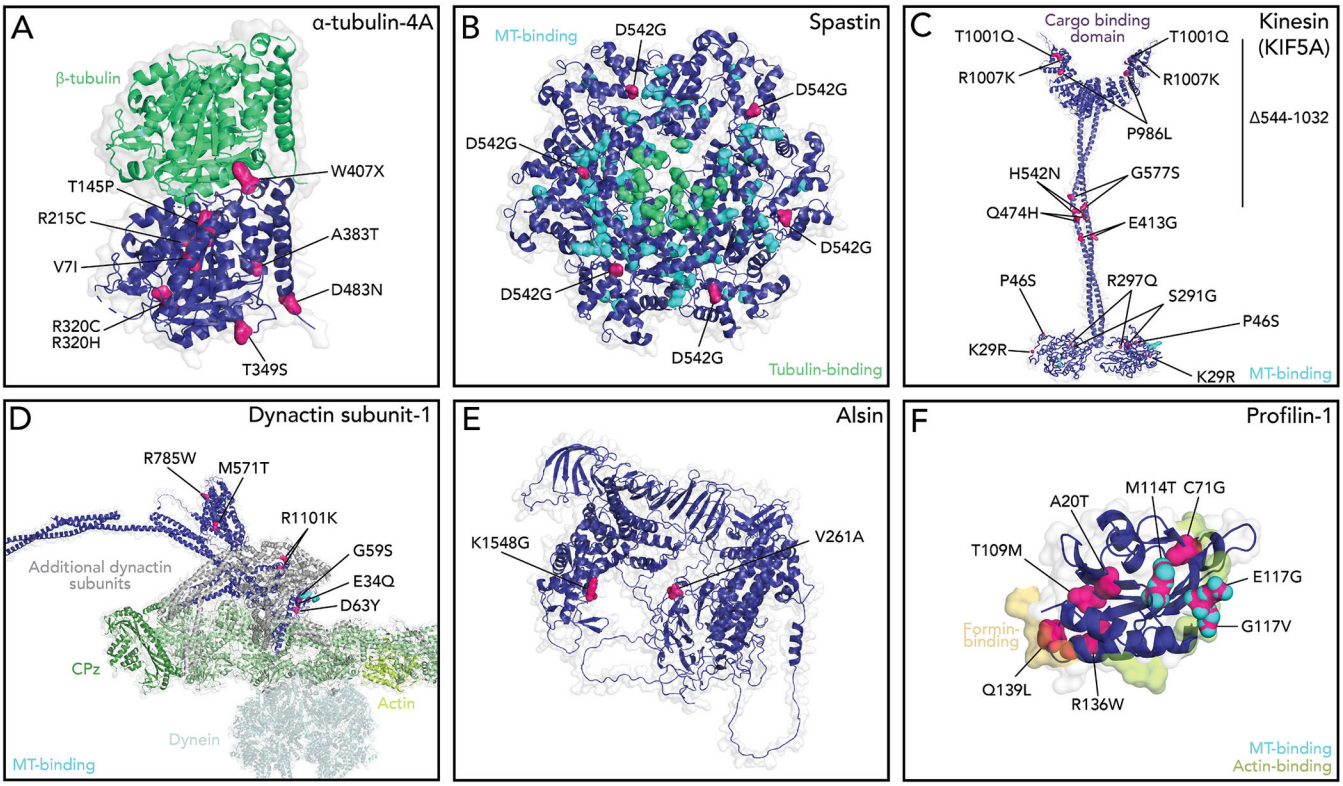

Fig. 2.

Positions of ALS-linked mutations in structures of cytoskeleton associated proteins. Cytoskeleton regulation proteins (dark blue) highlighting the positions of ALS-linked residues (pink). (A) α-tubulin relative to β-tubulin in the α/β heterodimer are shown (green). PDBID: 5KMG. (B) ALS residues in the spastin homohexamer. S44L and R65H residues are not present in the available structure. Microtubule (teal)- and tubulin-binding (green) residues are highlighted. PDBID: 6PEN. (C) General features of kinesin with the KIF5A motor domain. Microtubule binding residues (teal) are highlighted. Modeled after (Vale, 2003). PDBIDs: 4UXY, 1GK4, 3NF1. (D) View dynactin subunit-1 (DCTN1), with microtubule binding residues highlighted(teal). PDBIDs: 5NVU, 6ZNL, 2COY, 4RFX, 3E2U; and Alpha-fold ID: Q14203 (Jumper et al., 2021). (E) Alsin (ALS2). Alpha-fold ID: Q96Q42. (F) Profilin-1 and relevant binding surfaces to actin (lime green), formin proteins (yellow), and microtubules (teal) highlighted. PDBID: 2PAV.

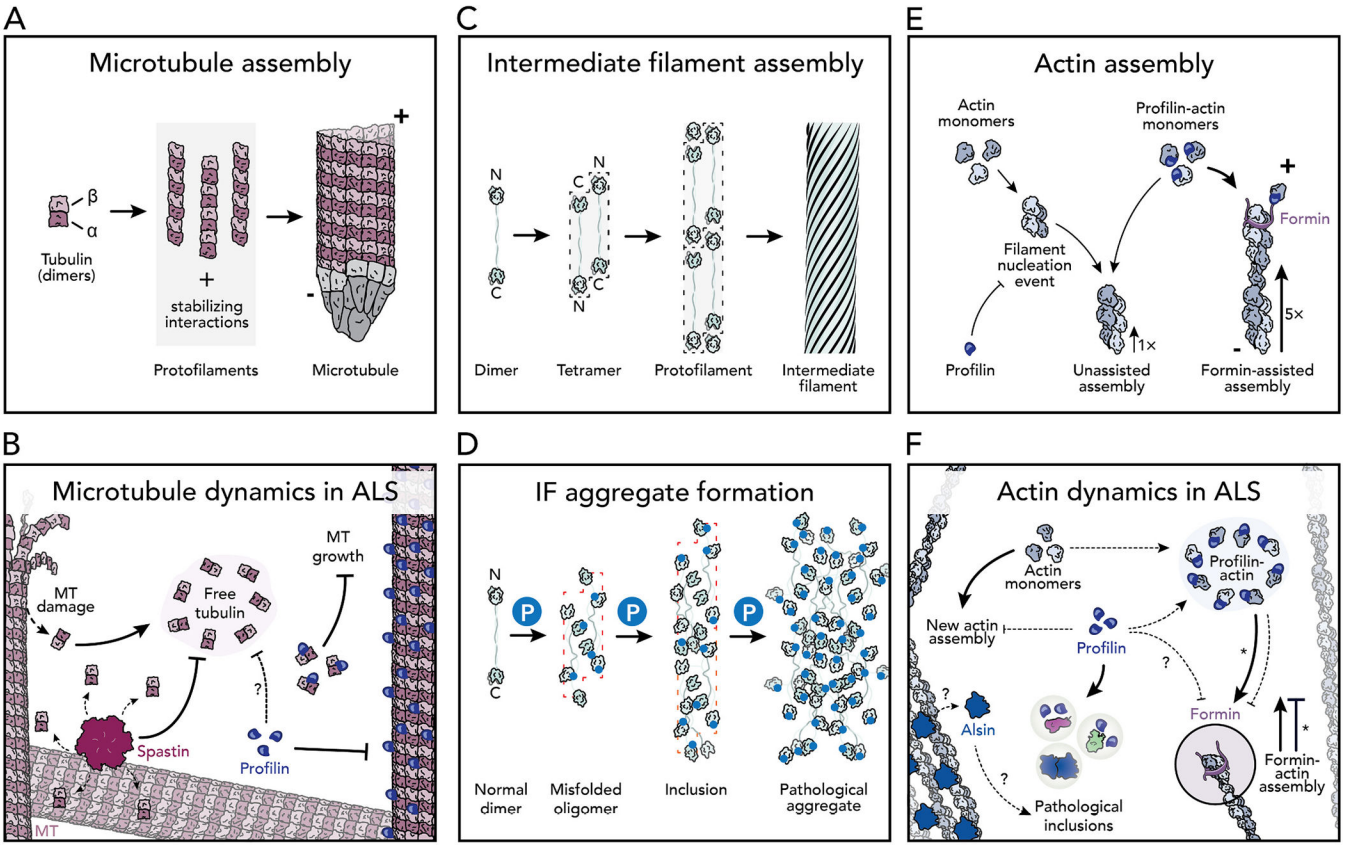

Fig. 3.

Mechanisms of cytoskeletal dynamics in the normal and predicted ALS-states. (A) Microtubule assembly. Dimers of α- and β-tubulin self-assemble to form protofilaments. Protofilaments are stabilized by ɣ-TuRC. Polarity: +, plus-end; −, minus-end. (B) Spastin (pink) disassembles microtubules excising subunits from the microtubule lattice. Profilin variants (dark blue) lose the affinity to bind to microtubules and possibly tubulin dimers, thereby destabilizing microtubule dynamics in ALS. (C) Intermediate filaments assembly. (D) Neurofilament and peripherin intermediate filaments become hyperphosphorylated (blue P), triggering the formation of pathological aggregates. (E) Actin filament assembly. PFN1 inhibits filament nucleation, but not the elongation rate. Formin proteins further stimulate actin elongation with PFN1. Polarity: +, plus-end; −, slower minus-end. (F) Profilin-mediated actin assembly mechanisms are disrupted in ALS including: reduced affinity for actin monomers and reduced formin-actin assembly. Asterisks note that the M114T and G118V profilin mutations enhance, rather than hinder, formin activities (Liu et al., 2022; Schmidt et al., 2021). Alsin (ALS2) association with actin is thought to be lost in ALS.

Table 1

Summary of mutations identified for ALS-associated cytoskeleton genes.

Gene	Abbrev.	ALS-associated variants	Genetics	Prevalence	Refs.
Alsin	ALS2	V261A; K1548G	AR	0.007%	(Yang et al., 2001; Hadano et al., 2001)
Dynactin subunit-1	DCTN1	E34Q; G59S; D63Y; M571T; R785W; R1101K; T1249I	AD	0.4%	(Puls et al., 2003; Münch et al., 2004; Stockmann et al., 2013; Münch et al., 2005)
Kinesin family member 5A	KIF5A	K29R; P46S; S291G; R297Q; E413G; Q474H; H542N; G577S; P986L; T1001Q; R1007K; Δ544–1032[†]	HM & SV	0.2%	(Nicolas et al., 2018; He et al., 2020)
Neurofilament	NF	A380T; deletions: Δ528–561; Δ655–662; Δ663–668; Δ663–677; Δ743–748; Δ790; insertion: 714[‡]	DLOF & IM	0.18%	(Cirulli et al., 2015; Corbo and Hays, 1992; Hirano, 1991)
Peripherin	PRPH	R133P; D141Y[‡]	DLOF	0.04%	(Gros-Louis et al., 2004; Leung et al., 2006; Corrado et al., 2011)
Profilin-1	PFN1	A20T; C71G; T109M; M114T; E117G; G118V; R136W; Q139L	AD	2.5%	(Wu et al., 2012; Ingre et al., 2013; Tiloca et al., 2013)
Spastin	SPAST	S44L[§]; R65H[§]; N542G	AD	0.02%	(Münch et al., 2008; Meyer et al., 2005; Brugman et al., 2009)
α-Tubulin 4A	TUBA4A	V7I; G43V[§], T145P; R215C; R320C; R320H; A383T; W407X; D438N	AD & NS	1.4%	(Smith et al., 2014; Pensato et al., 2015)

Abbreviations: AR, autosomal recessive; AD, autosomal dominant, HM, heterozygous missense; SV, splicing variant; DLOF, dominant loss of function; IM, insertion mutant; NS, nonsense mutation.

[†]Fig. 3B illustrates a general kinesin structure, however the motor domain used is from KIF5A (PDBID:3KIN).

[‡]No experimental structural information is available.

[§]Residue not present in the structure used in Fig. 3D.