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Chapter 12
The Cytoskeleton as a Modulator of Aging and Neurodegeneration

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1 Introduction

The cytoskeleton is a cellular entity, encompassing a multitude of filamentous proteins, forming structures that impart mechanical strength, allow intracellular transport and spatial organization, connect the cell to its environment, and generate forces that permit movement [1]. The ubiquitous nature of the cytoskeleton and the breadth of its functionality make it one of the most fascinating aspects of cellular biology, as well as one that is always worth considering when researching or discussing phenomena that affect the cells. In this review, we discuss the relevance of the cytoskeleton to the processes of aging and neurodegeneration, and provide examples that demonstrate its importance.

1.1 Components of the Cytoskeleton

Three types of cytoskeleton polymers have been defined: actin microfilaments, microtubules and intermediate filaments [1, 2]. We briefly describe their structure and function below.

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1.1.1 Actin Microfilaments

Actin filaments (also commonly referred to as F-actin) are about 7 nm in diameter and consist of monomers of globular (G-actin) that interact head-to-tail with each other. G-actin can bind ATP, and this promotes its polymerization to F-actin. ATP is subsequently hydrolyzed to ADP. Actin filaments are polarized with a positive (+) and negative (−) end. Polymerization can occur at both ends but is significantly faster at the + end. The filaments can organize into higher order structures with the help of crosslinkers (Fig. 12.1). Highly aligned actin bundles are responsible for the formation of narrow cell protrusions, such as filopodia, while highly branched bundles take part in larger cellular movements, such as those that occur in phagocytosis. The polarity of the filaments also allows them to support a family of ATP driven motor proteins, the myosins, that contribute to actin network organization and force generation [1, 2].

In neurons, actin forms patches in the initial segment of the axon and at points along its length [3, 4]. It also forms, in association with the actin capping protein

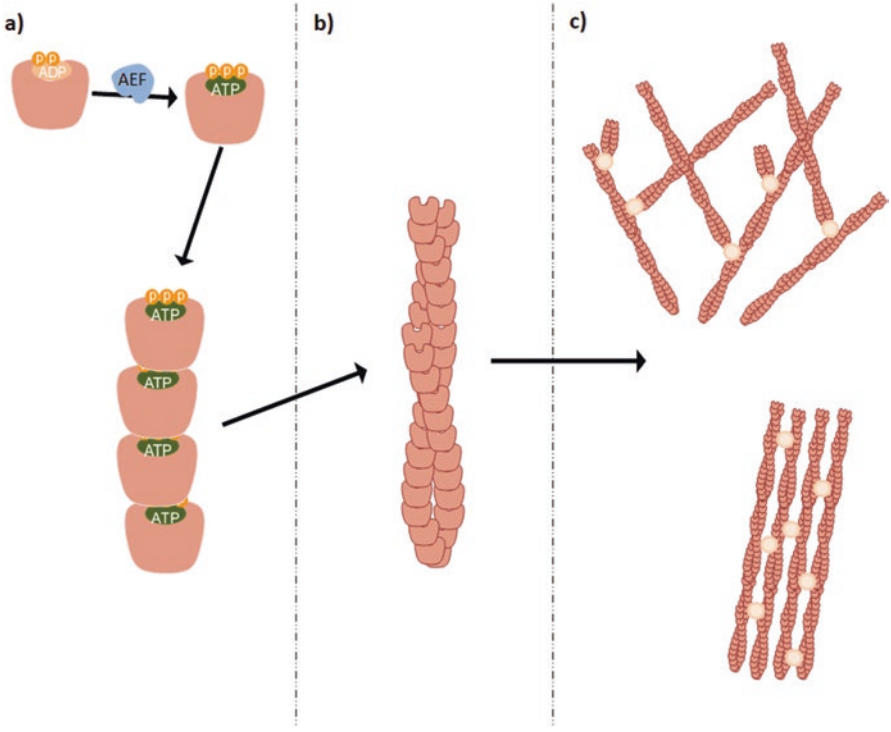

Fig. 12.1 Organization of actin microfilaments. (**a**) G-actin polymerization. Actin monomers are loaded with ATP with the help of a protein with ATP exchange factor (AEF) activity. This induces their polymerization. (**b**) F-actin. (**c**) Larger scale F-actin organization facilitated by crosslinker proteins

adducin, a series of periodic rings spaced by spectrin that are wrapped around the axonal shaft [5]. Actin is also a major contributor the motility and guidance of the neuronal growth cone. The growth cone has three domains: the central (C), the peripheral (P) and the transition (T) domain [6]. Actin is rich in the P and T domain and its polymerization and recycling allows for the formation of exploratory filopodia. In addition, myosin 2 generates forces that assist in propelling the growth cone forward and steer it towards its targets. Inhibition of these functions does not prevent axonal growth but it significantly reduces its speed and abolishes its ability to respond to guidance cues [7, 8]. It can also act as the driving force for axonal branching, as actin filament patches can initiate the formation of protrusions that subsequently are invaded by microtubules to create new collateral branches that allow the same axon to interact with multiple targets [9]. Furthermore, actin has been connected to synaptic signaling, as it has been implicated in the regulation of synaptic vesicle pools, vesicle docking to the active zone, and even endocytic retrieval of vesicle membranes [10]. Finally, actin contributes to dendritic spine organization [11–13] and, in collaboration with microtubules and the receptor-associated protein gephyrin, contributes to postsynaptic receptor clustering [14].

In oligodendrocytes, the glial cells that are responsible for myelinating the axons of the CNS to facilitate fast action potential conduction, the actin cytoskeleton plays a critical role by allowing these cells to alter their morphology during development [15]. These cells possess protrusions with actin rich filopodia and lamellipodia. Actin in these structures is organized in a fashion mostly similar to growth cones [16]. It acts as a necessary driving force that allows these protrusions to extend towards their target axons and wrap around them [17–20]. Subsequently, actin depolymerization allows these protrusions to convert into sheets by reducing surface tension, enabling proper myelin spreading [19].

1.1.2 Microtubules

Microtubules (MTs) are cylindrical bundles of parallel protofilaments comprised of α- and β- tubulin. These bundles can have 10–16 individual filaments, with 13 being the most common. They have a typical diameter of about 25 nm. Both tubulins can bind GTP, which promotes polymerization, but eventually hydrolyze it to GDP, weakening their affinity. This leads to what is described as “dynamic instability”, as microtubules can switch between stable growth and rapid depolymerization. Microtubules are polarized, with a + and a − end. This polarity becomes particularly apparent during a phenomenon known as treadmilling, during which tubulin is simultaneously removed from the − end of the filament and polymerized to the + end (Fig. 12.2). This polarity also allows microtubules to support ATP driven motor proteins, the kinesins and dyneins, which are responsible for the guided transport of cellular cargo. Microtubules interact with a group of proteins known as MAPs (microtubule associated proteins) that influence their stability and interactions with other cellular components. A subset of MAPs, the +TIPs (plus-end-tracking proteins) interact specifically with growing microtubule ends. There are also − end

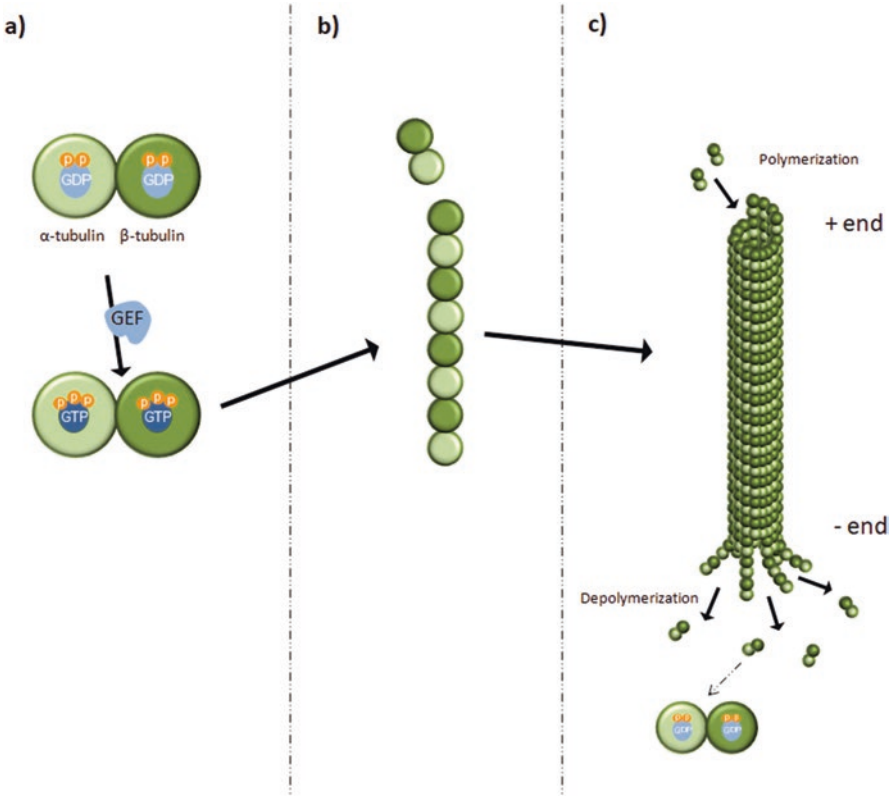

Fig. 12.2 Organization of microtubules. (**a**) GTP is loaded to α- and β- tubulin with the help of a protein with GTP Exchange Factor (GEF) activity. (**b**) A tubulin filament. (**c**) Microtubule structure and dynamics

capping proteins that can prevent depolymerization. Microtubule nucleation often needs to start at a Microtubule organization center (MTOC) where γ-tubulin interacts with α- and β- tubulin, providing a base for the start of filament extension [1, 2, 21]. The MTOC of mammalian cells is known as the centrosome. It consists of two perpendicular tubulin structures known as centrioles that are surrounded by a centrosomal matrix of proteins involved in microtubule nucleation, anchoring and release. The duplicated centrosome is responsible for the formation of the mitotic spindle, the microtubule structure that segregates chromatids during cell division [22].

In mature neurons, microtubules are arranged with the − end towards the cell body and the + end extending outwards, along the axon. They are discontinuous, with multiple start and stop sites [21]. In this context, there is evidence that microtubules cease to rely on the centrosomal MTOC for their organization [23, 24]. Axonal microtubules extend into growth cones, where they localize primarily in the C domain. However, they can extend even further and they are known to interact

with actin, particularly actin bundles that form filopodia in the P zone [6]. These microtubules have dynamic ends and are crucial to growth cone steering [25]. Outside of the growth cone, in cases of interstitial axonal branching formation, some axonal microtubules are reorganized and interact with the newly forming protrusion [26]. Microtubules also extend between the cell body and dendrites. In this case they adopt a mixed orientation, with + and − ends facing towards both directions [27].

1.1.3 Intermediate Filaments

Intermediate filaments (IFs) constitute a diverse family of cytoskeletal proteins that are expressed differentially across cell types. All of these proteins share structural similarity and organize in similar ways to provide mechanical strength and stability to most cell types, especially against tensile forces. IF subunits consist of a globular N-terminal head, an α-helical core and a variable C-terminal domain. Intermediate filament monomers tend to coalesce in pairs, forming parallel coiled coil dimers. Two antiparallel dimers can also associate to form a tetramer (Fig. 12.3). The higher scale organization depends on the tissue and the actual filament components but typically leads to a filamentous polymer of ~10 nm in diameter. Examples of IFs include keratin, vimentin, the lamins of the nuclear skeleton, α-internexin, peripherin, synemin, nestin or the light, medium and heavy neurofilaments (NF-L, NF-M and NF-H, respectively). Intermediate filaments are not polarized and therefore do not support molecular motors [1, 2, 28, 29].

Neuronal intermediate filaments (which will be referred as neurofilaments or NFs from now on) represent the main cytoskeletal element of mature neurons. They consist of NF-L, NF-M, NF-H and occasionally α-internexin and peripherin, with

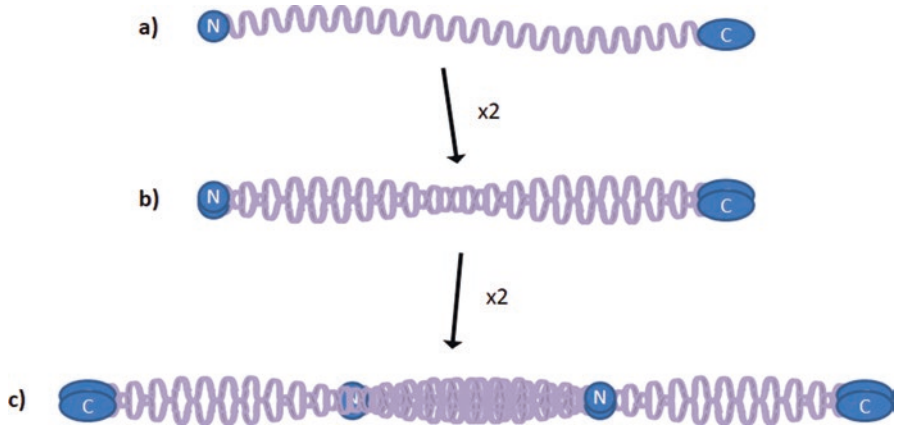

Fig. 12.3 Intermediate filament organization. (**a**) Monomer. (**b**) Dimer of parallel monomers. (**c**) Tetramer of antiparallel dimers

the actual composition varying by organism or even stage of development. The NF-M and NF-H C-terminal domains are notable for the presence of a large number of lysine-serine-proline (KSP) repeats that represent targets for regulatory phosphorylation. Neurofilaments reside in axons and act as regulators of axonal caliber, which has implications in myelin thickness and the rate of axonal conduction. They are also associated with axonal growth and regeneration [2, 29, 30].

2 The Importance of the Cytoskeleton to Aging and Neurodegeneration

2.1 Cytoskeleton and Organismal Aging

There is ample experimental evidence connecting the cytoskeleton with the processes of cellular and organismal aging. In yeast, actin has emerged as a regulator of lifespan by regulating the inheritance of mitochondria. During budding, actin cables create a retrograde flow from the bud towards the mother cell, driven by polymerization and myosin activity. This flow pushes mitochondria away from the bud, forcing them to "swim upstream" and ensuring that only healthy mitochondria can reach the new cell, granting it a longer lifespan and healthspan [31, 32].

In C. elegans, the actin cytoskeleton has been observed to deteriorate with aging. HSF-1, the master regulator of the heat shock response that provides thermotolerance and also contributes to organismal longevity, has been shown to act against this deterioration. This effect is mostly mediated through the upregulation of the expression of the calcium binding protein PAT-10. Most notably, loss of pat-10 is sufficient to decrease organismal lifespan and thermotolerance, while overexpression enhances thermotolerance and promotes longevity [33, 34].

In mammals and particularly in humans, oocyte fertility is reduced in aging. This is in part due to deterioration of meiotic spindle integrity. Spindle microtubules lose their ability to accurately interact with meiotic chromosomes and separate them, thus causing aneuploidies. The deterioration of the spindle can be attributed to the reduced activity of enzymes that are responsible for centrosome and microtubule maintenance [22, 35]. Centrosome defects have also been proposed as a possible explanation for the age-related decline of stem cell division [36].

The myelin sheath is crucial to adult neuron performance. Unfortunately, even healthy aging is accompanied by the emergence of defects in myelin composition and structure [37–39]. Thus maintenance mechanisms need to be activated to protect the axons. In the case of CNS oligodendrocytes, there is evidence indicating that the cytoskeleton is a fundamental constituent of these processes. Septins, a family of cytoskeleton associated scaffold proteins, have been shown to form filaments along with anillin in mice that support the myelin sheath and loss of these proteins leads to defects in myelin structure [40]. Additionally, it has been shown that de novo myelination pathways in the CNS remain active in adulthood through

new oligodendrocytes [41–43], the maturation of which is guided by cytoskeleton dynamics. This de novo myelination has been mostly associated with plasticity related adaptations but could also participate in maintenance.

In humans, aging is associated with increased aortic stiffness. This is often considered to preclude myocardial infarction, renal disease or even cognitive decline. A significant part of this aortic stiffness is attributed to vascular smooth muscle cells and particularly to their non-muscle actin cytoskeleton that is responsible for their connection to the extracellular matrix. Decoy peptides that inhibit actin polymerization or the interaction of the actin associated proteins talin and vinculin have been shown to be a potential method for counteracting aortic stiffness [44].

Another issue that emerges with human aging is the deterioration of heart health. Heart failure in particular is one of the most prominent causes of death and disability in the elderly [45]. Actin is critical to heart health, as actin fibers constitute a major component of sarcomers, the mechanical units that drive cardiomyocyte contraction [46]. Experiments in mice and rats have shown a conserved activation of actin remodeling by vinculin during aging. Further experiments in Drosophila have suggested that this is an anti-aging mechanism that improves heart function and overall organismal lifespan [47]. Actin is also relevant to heart health due to its association with the proliferative capacity of cardiac fibroblasts. Aging fibroblasts exhibit reduced levels of the LOX-1 receptor, lose their proliferative capacity and exhibit a disorganized actin network. Restoration of LOX-1 levels re-establishes fibroblast proliferative potential and reinstates actin organization [48].

2.2 Cytoskeleton and Neurodegeneration

Considering the prominent presence and important functionality of cytoskeletal proteins in neurons, it comes as no surprise that they have also been heavily implicated over the years in processes underlying their dysfunction. Below, we discuss experimental data that connects the cytoskeleton to neurodegenerative diseases, as well as injury induced neurodegeneration.

2.2.1 Tau Associated Pathologies

Alzheimer's disease (AD) is characterized by extracellular deposits of Aβ peptides and intracellular filamentous aggregates of Tau, a major microtubule associated protein [49–52]. Beyond AD, Tau aggregation has emerged as a common form of phenomenon in more than 20 different types of neurological disease, including Pick's disease, progressive supranuclear palsy, chronic traumatic encelopathy, argyrophilic grain disease, frontotemporal dementia with parkinsonism-17, corticobasal degeneration and Parkinson's disease (PD) [49, 53]. In the human brain, Tau has six isoforms with either 3 or 4 microtubule binding repeats at its C-terminal domain (3R and 4R Tau respectively) [49, 54, 55]. The protein is typically a dipole but

post-translational modification, especially phosphorylation, can affect its charges and disrupt its ability to bind microtubules [56–58]. In addition to its microtubule binding abilities, it has been shown to interact with the plasma membrane [59]. It is also capable of interacting with actin, induce its polymerization and promote microtubule and actin co-alignment [60].

Tau assembles into filaments through its repeats forming a cross-beta structure. Thus, the microtubule binding regions are trapped in the core of the aggregate, rendering physiological interaction with microtubules impossible [61–64]. Tau aggregates are commonly referred to as Neurofibrillary Tangles (NFTs), but their actual morphology can vary across different diseases, leading to their sub-characterization into paired helical filaments (PHFs), straight filaments (SFs) and twisted ribbon-like lilaments (TRFs) [49, 51]. Tau is abnormally hyperphosphorylated in all of its aggregates. This has led to the belief that phosphorylation is toxic and induces Tau aggregation. However, this might not be the case as human tauopathies have not been linked to defects in kinases or phosphatases, and kinase inhibition has not been shown to be an effective treatment option [49, 51]. Furthermore, there is evidence of Tau phosphorylation acting in a benign fashion in the process of hibernation [65, 66], without fibril formation and with reversibility.

There are several possible explanations on the causes of Tau associated neuropathology; Tau aggregation could lead to an effective LoF phenotype by preventing the protein form exercising its normal roles [67]. For instance loss of Tau in mouse models of AD (over-expressing mutant APP, the precursor of the Aβ peptide) aggravated neurodegeneration and exhibited axonal swellings full of cellular debris and mislocalized organelles, vesicles and even presynaptic terminal components [68]. In addition, Tau KO mice exhibit intracellular iron accumulation, substantia nigra neurodegeneration, brain atrophy and parkinsonism. Supplementation with an iron chelator rescued this phenotype. These observations were attributed to reduced transport of APP onto the neuronal membrane (APP in conjunction with ferroportin acts as the sole iron export system in neurons) due to the altered microtubule dynamics that arise from lack of Tau [69]. Another indication supporting this idea is the observation that microtubule stabilizing drug treatment has had some effectiveness in ameliorating tauopathy [70–72]. An alternate explanation could be that Tau (normal, mutant and/or phosphorylated) represents a toxic threat to cells in a gain of function (GoF) fashion. The protein has, for instance, been implicated in the disruption of mitochondria through the induction of mitochondrial fusion, inhibition of mitophagy and a reduction of ATP production [73, 74]. There are indications suggesting that a GoF threat might arise from non-filamentous forms of Tau [51], as experiments have demonstrated that truncated/cleaved Tau can be toxic [75, 76]. In addition, neurodegeneration can occur before or without Tau filament formation [77, 78] and tangle formation can persist in rescued animal models [79]. In the latter case, NFT formation might act as an attempt from the cell to quarantine dangerous Tau forms. Arguably, it is possible that both explanations are true on a disease by disease basis, or even simultaneously, with aggregation acting as the “lesser evil” that initially protects neuronal cells from toxicity but eventually ends up being deleterious through dysregulation of the cytoskeleton or other effects.

The aforementioned Tau-actin interaction [60] might have a functional implication in neurodegenerative disease, as experiments in Drosophila melanogaster and have shown that mutant forms of Tau associated with human tauopathies are capable of inducing the formation of actin rich structures resembling Hirano bodies (actin aggregates that occur in human patients). Actin was necessary for Tau toxicity in these instances. Tau phosphorylation, as well as transgenic Aβ42 expression, exacerbated actin aggregation and neuronal death [80]. Recently it was reported that tau can accumulate and form tangles in the medial temporal lobe and particularly in the entorhinal cortex as a pure consequence of normal "healthy" aging indicating a possible mechanism for the aging-associated loss of episodic memory [81].

2.2.2 Other Microtubule Associated Pathologies

The implication of microtubules in neurodegenerative disease extends beyond the role of Tau. Part of the neurotoxicity in Huntington's disease (HD) can be attributed to defects in microtubule based axonal transport, and MT stabilizing acetylation is potentially beneficial [82]. Very similar observations have been made in a model of Charcot-Marie-Tooth disease (CMT) [83]. Experiments in a PD model have shown that intracellular transport could be disrupted due to the reduction of microtubule dynamics, and that this might preclude mitochondrial damage and caspase 3 activation [84]. Disrupted mitochondrial dynamics, along with reduced levels of MAP expression, can also be observed in amyotrophic lateral sclerosis (ALS) patients and models, and pharmacological MT stabilization can delay the progression of the disease in mice [85–87].

2.2.3 Actin Associated Pathologies

ALS is a neurodegenerative disorder associated with the loss of motor neurons in the cerebral cortex, the brainstem, and the ventral horn of the spinal cord [88]. The disease is mainly linked with alterations in genes such as superoxide dismutase 1 (SOD1), fused in sarcoma (FUS) and TAR DNA binding protein (TARDBP / TDP-43) [89]. Spinal muscular atrophy (SMA) is a disorder with phenotypical similarity to ALS that exhibits motor neuron loss exclusively in the ventral horn of the spinal cord [88]. SMA is attributed to loss of function (LoF) of the survival of motor neuron 1 gene (SMN1) [90]. Both ALS and SMA have been linked with altered cytoskeletal dynamics or mutations in known regulators of the cytoskeleton [91–97]. Notably, the actin regulators profilins have been implicated in both diseases [93, 96–98]. Profilins are a family of proteins that can bind monomeric G actin and facilitate the exchange of ADP for ATP. Depending on the cellular conditions, profilins have been suggested to act as either a promoter of actin polymerization and F-actin stabilizer, or as a sequester of G-actin and F-actin destabilizer [88, 99]. Profilin binding activity can be inhibited through phosphorylation by the RhoA kinase (ROCK), an important regulator of actin dynamics [100, 101]. It has been

shown that SMN1 binding to profilin 2 reduces its inhibitory effects and promotes actin polymerization [93]. It has also been suggested that this binding protects profilin from ROCK phosphorylation and that the source of cytoskeletal defects in SMA is the loss of this protection [88]. In ALS, profilin 1 has been suggested to contribute to disease pathology through the formation of TDP-43 associated aggregates [97, 102, 103], through loss of its ability to interact with stress granules [104], or through dysregulation of actin dynamics [105, 106]. It is worth mentioning that profilin has also been shown to interact with the polyglutamate protein Huntingtin and inhibit its aggregation. The prevention of profilin inhibition by ROCK has also been demonstrated as a potential therapeutic approach for HD [101]. Beyond its aforementioned potential association with Tau, another connection of actin with AD pathology was revealed recently. The actin cytoskeleton was shown to be compromised in transgenic mouse models early in disease progression in conjunction with dendritic spine effects and a decline of AMPA signaling [107].

Microglia can act as a line of defense against AD by migrating towards extracellular Aβ42 aggregates, binding them and phagocytosing them. However during aging, Nogo/Ngr signaling reduces the ability of microglia to migrate and adhere to Aβ42 through Rho-GTPases that regulate actin dynamics and end up preventing protrusion extension and cell polarization [108]. On the other hand, the cytoskeleton might also have an inhibitory role in this interaction, as it has been reported that cytosolic phospholipase A2 (cPLA2), a factor that mediates the Aβ-induced response in glial cells, acts to reduce the cytoskeletal-membrane connectivity that represents a physical barrier against Aβ endocytosis [109].

Alterations in actin dynamics may also play a role in PD, as a-syn has been shown to inhibit cofilin, an actin destabilizer, in experimental models and patients. This leads to actin overstabilization, with potential negative implications for synaptic signaling [110]. Cdc42 is a Rho-GTPase that is involved in the regulation of actin dynamics. Some variants of variants of CMT have been associated with a mutation in Frabin, the GTP exchange factor of Cdc42 [111, 112].

2.2.4 Neurofilament Associated Pathologies

Neurofilaments have also been associated with neurodegenerative disease. Abnormal neurofilament aggregation has been observed in various disorders, such as AD, PD, CMT and ALS. It seems to be connected with deviations from the exact correct NF component stoichiometry, as it can occur in response to both down-regulation or up-regulation of individual NF genes [113–115].

In AD, neurofilaments are another major component of Tau NFTs [116]. In these tangles, they adopt a paired helical filament conformation [117], and exhibit extensive levels of phosphorylation [118].

Neurofilaments are also a primary component of the Lewy bodies, the characteristic protein inclusions of PD [119, 120]. They are extensively phosphorylated in this instance as well [121]. Patient tissues exhibit down-regulation of NF-L and NF-H expression [122]. Mutations in the gene that codes NF-L have emerged as a

cause for CMT. These mutations lead to defects of axonal transport, neurofilament disorganization, and usually aggregation [123–131]. Some of the NF-L mutations that cause CMT lead to neurofilament aggregation due to the abolition of protective phosphorylation [129–132].

ALS is characterized by intraneuronalaxonal NF aggregation [133–135]. This is also the case in mice expressing mutant human SOD1, the gene mostly associated with familial cases of ALS [136]. This aggregation might be dispensable for the eventual progression of the disease [137] but its reduction might still be somewhat beneficial. Perhaps unexpectedly, overexpression of NF-H [138–140], or NF-L [138] or downregulation of NF-L [141] were all successful in imparting a partial protective effect that is attributed to a redirection of NF accumulation from the axon to the cell body/perikaryon. The exact mechanism of this protection is, however, uncertain.

2.2.5 Neurodegeneration Due to Injury

Injured axons of CNS neurons degenerate, in a process known as Wallerian degeneration. Fragmentation of microtubules is possibly the earliest step in this process [142]. Axons that are retracting due to injury exhibit a disorganized microtubule network [143]. In cases where axonal regeneration is possible (such as the peripheral nervous system), it is driven by microtubules and requires tubulin deacetylation, a modification that decreases their stability [144, 145]. The levels of expressed and axonally transported neurofilaments are also reduced, and are only restored in axons that can regenerate [146–154]. Microtubule destabilization accompanied by energy depletion precludes neurofilament defects, mitochondrial swelling and axonal degeneration. Artificial energy repletion is effective at stopping this process [155]. Dendrites also degenerate after injury. Experiments in D. Melanogaster showed that this requires microtubule severance by the ATPase fidgetin [156].

3 Conclusions

Despite decades of research, our knowledge on the cytoskeleton remains incomplete. There are still numerous questions that need to be addressed regarding cytoskeletal contributions to pathology. In this regard, the cytoskeleton represents a clear challenge for future research, and for the development of potential therapeutic strategies relevant to aging and neurodegeneration.

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