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Editorial

Special issue on 'Cytoskeletal proteins in health and neurodegenerative disease'

ABSTRACT

The cytoskeleton is the major intracellular structure that determines the morphology of neurons and maintains their structural integrity. It is therefore not surprising that a disturbance of cytoskeletal structure and functionunderlies many neurodegenerative diseases. This special issue brings together current information on the three majorneuronal cytoskeletal filament systems, microtubules, microfilaments and neurofilaments, and aims to provide a comprehensive overview of the role of the key components of these three systems under both physiological and pathological conditions. It therefore also addresses the role of microtubule-associated proteins (with a focus on tau) and motor proteins (with a focus on kinesin).

The cytoskeleton is a key component of every eukaryotic cell. It consists of protein polymers and a collection of associated factors that are organized in a network of filamentous arrays that interact in a dynamic manner. The cytoskeleton provides a structure that, on the one hand, is rigid, and on the other hand is responsive to a range of cues which allow it to be sufficiently plastic to facilitate a change in cell shape and, in some cases, cell movement. The cytoskeletal elements also interact with motor proteins that provide both the force and directionality that are needed for intracellular transport and mobility (Tuszynski et al., 2003).

In neurons, the cytoskeleton is tailored to meet the specific needs of this specialized cell type, which consists of a cell soma and two principal types of processes, the axons and the dendrites, which can extend a remarkable distance from the soma and develop a complex branching pattern depending on the type of neuron. The axon is separated from the soma by the axon initial segment, which provides an effective diffusion barrier. Dendrites are further compartmentalized based on the presence of dendritic spines that represent the post-synaptic compartment of most excitatory input Zhong et al. (2014). The dendrites and the soma comprise a relay station where incoming signals are integrated. Neurons maintain their peculiar structure and compartmentalization with the help of an internal dynamic cytoskeleton made up of different filament systems. The three main neuronal cytoskeletal structures discussed in this Special Issue are actin filaments (Nixon, Gallo), neurofilaments (Vickers) and microtubules (Baas, Gallo, Prokop). Associated with microtubules, and binding to them, are microtubule-associated proteins (MAPs), including the axonal protein tau (Arendt), and motor proteins, such as kinesin, which provides anterograde transport, and dynein, a retrograde transporter (Kins). Prominent proteins that interact with actin filaments and are considered to regulate microfilament structure are the tropomyosins (Fath) and drebrin (Gordon-Weeks).

A plethora of articles are available on selective aspects of cytoskeletal proteins but what has been lacking from the literature is a collection of review articles focusing on all of these major cytoskeletal elements and the proteins with which they are associated, as well as their function in health and disease. This Special Issue brings together nine review articles that present information on the role of the neuronal cytoskeleton under both physiological and pathological conditions, its interactions and its regulation, as detailed below.

(1) Microtubules serve as structural elements to allow axons and dendrites to obtain their specialized morphology. They also function as long-distance railways for the anterograde and retrograde transport of proteins and organelles. Peter Baas and Andrew Matamoros discuss the intricacies of microtubule dynamics and outline how the nucleation of microtubules occurs as well as the way in which the three forms of tubulin (α, β, and γ) differ (Baas). Microtubules are intrinsically polar structures, with β-tubulin being located at the plus and α-tubulin at the minus end; the motor dynein moves towards the minus end of the microtubule and most kinesins move towards the plus end. Facilitating microtubule organization in neurons, microtubule-interacting proteins are enriched in specific compartments, such as TRIM46 in the axon initial segment. The authors also discuss the puzzle regarding the source of neuronal microtubule stability. Although tau and other MAPs are traditionally seen as microtubule-stabilizing compounds, it is suggested (factoring in the millisecond on and off rate of these proteins) that they may be more important in regulating rather

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than conferring stability. Attention is also given to microtubule end-targeting proteins (such as EB3) and microtubule-severing proteins (katanin and spastin). Regarding motor proteins, the concept of a specific tubulin code, which seems to mark microtubules for defined interactions, is discussed. The final section of this review then discusses microtubule dysfunction in the context of disease (Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease). The authors suggest that, rather than exploring the potential of microtubule-stabilizing drugs, inhibiting microtubule-severing proteins might be the better approach for therapeutic interventions targeting microtubules.

(2) Andreas Prokop and colleagues specifically discuss the dynamics of microtubules, dissecting the cytoskeletal machinery into its conceptual sub-machineries and then assessing how these interface with each other (Prokop). The first section of this review addresses the role of microtubule dynamics in development and how this dynamic feature persists into adulthood. The second section provides an overview of the physical and biochemical properties of tubulin and how microtubules, the stiffest of all cytoskeletal polymers, form lattices. The various mechanisms regulating the dynamics of microtubules at the plus end are discussed and summarized in an integrating figure, highlighting the importance of how tubulin pools are controlled in axons. The article discusses this issue, delving into the transcriptional control of tubulin, the different modes of transport, microtubule stability and controlled degradation pathways. Up to a few hundred EB proteins can bind to the microtubule plus end with a very short dwell time, i.e. in a highly dynamic manner with a constant turn-over. These interactions are discussed, together with the various functions of the plus end. Finally, a section also addresses the influence of lattice-based mechanisms on the polymerization and depolymerization of microtubules, and reports on the post-translational modifications of microtubules that are often taken as indicators of microtubule stability, with detyrosination and acetylation correlating with stable fractions. As is also discussed by Matamoros and Baas (Baas), the mechanism by which MAPs act on microtubules is poorly understood. Prokop and colleagues present a model in which microtubules in mature axons are constantly renewed through steady state de/polymerization processes.

(3) Thomas Arendt and colleagues present a comprehensive overview of the 'neuronal' MAP tau, broadly covering its cell biology and central role in tauopathies including Alzheimer's disease (Arendt). The cell biology section covers tau haplotypes and the regulation of gene expression of this multiple isoform protein, providing structural insight into tau and its domains, its post-translational modification, with a major focus on phosphorylation, and its cellular functions (canonical in binding microtubules, non-canonical, and even non-neuronal). The second half of the review discusses all facets of tau pathology, initially focusing on Alzheimer's disease as 'the' tauopathy prototype, and then on tauopathies more generally, in which the tau pathology is not confined to neurons, but is also present in glial cells. The review contains 12 figures that are suitable for didactic purposes and four detailed tables, listing tau phosphorylation sites, the various tauopathies, a classification of tauopathies based on the predominant tau isoform, and the predominant cell-type-specific tau pathology in different tauopathies. In their conclusion, Arendt and colleagues point out that our appreciation of the role of tau in 'non-typical' compartments, such as the nucleus and spines, is only slowly unfolding. Furthermore, as they point out, how tau causes neurodegeneration is still not well understood. Another intriguing question is the biological significance of the large heterogeneity of tau isoforms, with tau being an apparently promiscuous molecule. Finally, determining how the two key lesions of Alzheimer's disease, tau and amyloid β (Aβ), interact, is important for developing treatment strategies, yet there is a still a lack of basic understanding in relation to this issue.

(4) In his review, Phillip Gordon-Weeks discusses the filamentous (F)-actin side-binding and bundling protein drebrin, which couples actin filaments to dynamic microtubules (Gordon-Weeks). This interaction has a critical developmental role during neuronal growth cone formation, as well as in the dendritic spines of mature neurons. As elaborated in the article, drebrin comes in two forms, an 'embryonic' drebrin E and an 'adult' drebrin A; however, their distinctive roles have not been fully dissected. The author suggests the use of super-resolution microscopy to better understand how drebrin is distributed in neurons and what governs its localization. He further discusses the various binding partners of drebrin, together with the functional domains in the protein that govern these interactions. A preferred partner of drebrin is EB3 that localizes to the growing plus end of dynamic microtubules. Evidence from cell biological studies and structural analyses are presented that indicate that drebrin stabilizes F-actin. In the case of spines, it is well known that the dynamic behaviour of F-actin and microtubules dominates dendritic spine changes in response to synaptic activity. Here, drebrin has an important role, influencing dendritic spine morphology by regulating F-actin, facilitating the activity-dependent accumulation of the scaffolding protein PSD-95 in the post-synaptic density, and distributing NMDA receptors. An interesting discussion is presented that focuses on activity-driven microtubule capture and insertion into dendritic spines. Whereas normally only approximately 1% of dendritic protrusions contain a microtubule at any time, the frequency of invasion, as well as the dwell time, are enhanced by activation, with EB3 being localized to the tip of these microtubules. In a disease context, drebrin loss, concomitant with an increase in the actin-severing factor cofilin, has been shown to precede synaptic loss in Alzheimer's disease. Drebrin loss can also be induced *in vitro* by incubation with Aβ oligomers. Cofilin activity is negatively regulated by the activity of LIM kinase that, interestingly, protects against Aβ-induced drebrin loss. As suggested, more work needs to be undertaken to investigate the drebrin/EB3 pathway, or any other pathway, that links dynamic microtubules and F-actin under physiological or pathological conditions.

(5) Next, Gianluca Gallo and Almudena Pacheco review the literature covering recent advances in our understanding of cytoskeletal interactions in neurons by focusing on the initiation of processes from neuronal cell bodies and the collateral branching of axons (Gallo). The authors come to the conclusion that the appreciation of the neuron as an integrated system remains a frontier of investigation. The review discusses differences in nucleation mechanisms that are more restricted for microtubules than for actin, with the majority of work being done *in vitro*. The authors discuss the evidence for cross-talk and interactions between actin filaments and microtubules in the growth cone and in axon branching and initiation, presenting the data in a historical overview. There is a section on MAPs, with the different forms of MAP2 and MAP1b all binding to both microtubules and actin. The fourth section discusses microtubule plus end-associated proteins (EB proteins, drebrin, CLIP-170, cytoplasmic linker protein-associated proteins (CLASPs), spectraplakins, neuron navigator 1 (NAV1) and adenomatous polyposis coli (APC)), after which additional regulators of cytoskeletal cross-talk and organization (septins, collapsin response mediator proteins (CRMPs) and doublecortin) are considered. The review then finishes with a mechanistic section on how microtubules are targeted into

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