An Issue on Concepts and Techniques for Cytoskeletal Proteins in Health and Neurodegenerative Disease

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Abstract

The field has advanced quickly since we put together a well-received special issue on "Cytoskeletal Proteins in Health and Neurodegenerative Disease" for Brain Research Bulletin in 2016. This is largely because new techniques, like super-resolution microscopy, have developed and matured. Since we were asked to make a sequel, we chose to stick with the main idea while emphasising new ideas and techniques. As before, we gathered nine papers on the function of the neuronal cytoskeleton in normal and abnormal circumstances. Throughout a neuron's lengthy existence, cytoskeletal components form and are maintained. Seven of the contributions present contemporary ideas and examine these topics, as well as how they may affect physiology and neurodegenerative illnesses. Two papers concentrate on unique methodological advancements and how these methods can be applied to examine the neuronal cytoskeleton's structure and function in novel ways. The collection of articles shows that in order to adequately explore the causes and consequences of the role of cytoskeletal proteins in health and disease, future approaches must take into account the functional relationships between the individual filament systems as well as the influence that various signal transduction mechanisms have on the cytoskeleton and vice versa. In order to test important field hypotheses, we believe that this compilation will aid in the design of appropriate studies using innovative techniques.

Keywords: Cytoskeletal proteins • Neurodegenerative • Neurofilaments

Introduction

The specialised and highly sophisticated cells called neurons. They take on a distinctive morphology that includes a long axon, numerous collaterals, and highly branching dendrites. This morphology forms the structural foundation for the function of neurons as fundamental information-processing units. According to Trushina et al. (2019), the primary intracellular element that provides the structural foundation for neuronal shape and function is the cytoskeleton [1]. As a result, the three cytoskeleton filament structures—microfilaments, intermediate filaments, and microtubules—are highly specialised in neurons where they play a crucial role in process formation, cellular polarity development, and maintenance of neuronal plasticity. In healthy neurons, related proteins exert strong temporal and spatial control on the assembly and operation of the cytoskeletal components. Two papers concentrate on unique methodological advancements and how these methods can be applied to examine the neuronal cytoskeleton's structure and function in novel ways. The collection of articles shows that in order to adequately explore the causes and consequences of the role of cytoskeletal proteins in health and disease, future approaches must take into account the functional relationships between the individual filament systems as well as the influence that various signal transduction mechanisms have on the cytoskeleton and vice versa. In order to test important field hypotheses, we believe that this compilation will aid in the design of appropriate studies using innovative techniques.

The authors talk about how actin-binding proteins influence actin dynamics because spatially and temporally controlled microfilament dynamics is essential for axon navigation throughout nervous system development. Additionally, Cyclase-Associated Proteins (CAPs), which were recently revealed to be involved in growth cone function and have been linked to the aetiology of human disorders through genetic research, may have a role to play in this (Rust and Marcello, 2022). In their article, the authors expand on their discussion of new instruments and methods for figuring out how microfilament regulation in growth cones works. These include Stimulation Emission Depletion (STED) and single molecule localization microscopy (SMLM), which produces images with a resolution of under 20 nm [1].

In addition to microfilaments, microtubules are also essential for process creation and constitute the primary pathway for axonal transport in neurons. Eckel et al. (2023) and Pinho-Correia and Prokop (2023) in this issue concentrate on the development, structuring, and upkeep of the microtubule system in neurons [2-4]. Axons can develop processes that extend more than a metre from the neuronal cell body and can be incredibly lengthy. Since faulty microtubule bundles can result in axonal transport blockage, this places great demands on the local regulation of microtubule polymerization, posttranslational modifications, and maintenance of a functional axonal microtubule array. The potential contribution of an active recycling procedure involving the reversal of posttranslational changes, the exchange of GDP for GTP, and a putative quality control mechanism for tubulin heterodimer repair is discussed by Pinho-Correia and Prokop. It's possible that chaperones like those found in the Tubulin-Specific Chaperone Complex (TBC) are involved in this process, but as the authors point out, the topic is both understudied and underrepresented in the literature. Given that too much tubulin can be hazardous and that mutant tubulins that are incapable of polymerizing have been linked to sickness in humans, this lack of deeper understanding may also hinder our ability to understand neural diseases.

Microtubules have a distinctive and compartment-specific polarity orientation in neurons. While they are primarily evenly orientated in the axon with their plus (or rapidly growing) end towards the tip, they are oriented in dendrites in a mixed polarity fashion. Eckel et al. (2023) discuss the possibility that microtubule polarity defects could significantly contribute to neurodegeneration in this issue [5]. The speed and dependability of motor-based organelle transport are negatively impacted by even minor variations in the normally uniform plus-end-out microtubule polarity pattern in axons, as demonstrated by the authors using mathematical modelling. They contend that more research is required to explore the potential that this pathway contributes to nervous system deterioration in illness.

The third and most frequently disregarded filament system in neurons are intermediate filaments. They have a diameter that falls somewhere between microtubules and microfilaments. They also exhibit the least dynamic behaviour among the three filament systems. The neurofilaments, which are intermediate filaments peculiar to neurons, are a highly linked, exceptionally stable structure that shows a high degree of post-translational alterations that may have an impact on how they function in both health and illness. The tau protein is altered in neurodegenerative illnesses like AD by many of their posttranslational changes, including phosphorylation, glycosylation, nitration, oxidation, and ubiquitination. However, there is still another layer of control, and in this special issue Yuan and Nixon (2023) give a thorough description of the post-transcriptional regulation of neuro filament proteins.

They formulate the hypothesis that neuro filaments and tau in AD may be connected by RNA-mediated processes such as alternative splicing and posttranscriptional regulation of neuro filament and tau protein expression by RNA-binding proteins and microRNAs. This point of view, which concentrates on the enzymes that might be dysregulated upstream of both tau and neuro filaments, may help to provide a more comprehensive understanding of neurodegenerative processes.

Additionally, it has become clear that inflammation has a role in almost all neurodegenerative illnesses, which again puts the spotlight on non-neuronal cell types in the brain. This includes astrocytes, which have the capacity to create morphologically altered pro inflammatory phenotypes. Therefore, it is not surprising that cytoskeletal rearrangements play a significant role in their phenotypic and functional changes. It has also been demonstrated that in microglia, another type of glial cell type involved in neuro inflammation, the formation of stable acetylated and detyrosinated microtubules is closely linked to the change from an amoeboid to a ramified phenotype. Villablanca et al. (2023) provide a summary of alterations in the astrocytes' three cytoskeletal systems—microtubules, microfilaments, and the intermediate filament system—as well as the relationship between these modifications and pathology and ageing [6]. Surprisingly, GFAP overexpression is not only a marker for reactive astrogliosis, but also for ageing in mice and people. Additionally, ageing can have an impact on the dynamics of astrocyte microtubules and microfilaments. According to the authors, cytoskeletal dynamics are linked to the proinflammatory secretory phenotype seen in reactive astrogliosis and senescence, whereas changes in the posttranslational modifications of tubulin are linked to the proinflammatory characteristics of astrocytes. They contend that finding new targets for neuroinflammation may be aided by a clearer comprehension of the astrocyte cytoskeleton's regulating function. Tau, which controls neural plasticity and genomic stability, is a prime example of a single cytoskeletal protein involved in the onset and progression of neurodegenerative illness. More than twenty disorders, including AD and the major tauopathies progressive supranuclear palsy, corticobasal degeneration, and Pick's disease, are also impacted by the protein [7-11].

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