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Membrane trafficking and cytoskeletal dynamics in neuronal function

1. Introduction to the special issue

The complex architecture of neuronal cells is fundamental to function, yet exerts a high demand on the processes that underlie the trafficking of material to the correct subcellular destination. To maintain cellular homeostasis, and to rapidly accommodate to environmental signals or synaptic activity, neurons are endowed with a complex cellular machinery that allows the trafficking of material to their correct subcellular destination. Receptors, ion channels, adhesion complexes, and other membrane components are synthesized and processed in a series of intracellular compartments, including the endoplasmic reticulum (ER) and the Golgi network, before they are actively trafficked to the membrane via transport vesicles. These processes are intimately controlled by cytoskeletal dynamics that allow and guide long-range transport of vesicles to their correct subcellular destination, control local morphological changes, and compartmentalize local signaling events. Recent advances in the field allow the study of trafficking events and cytoskeletal dynamics at high spatial and temporal resolution, and have rapidly expanded our understanding of how membrane trafficking and cytoskeletal dynamics control key neuronal processes such as molecular transport, polarity, signaling, and plasticity. In this Special Issue "**Membrane trafficking and cytoskeletal dynamics in neuronal function**" sixteen reviews highlight some of the most exciting new insights in the dynamic molecular processes that are so fundamental to neuronal development and functioning, and present emerging concepts on how disruptions in these processes can lead to neurological disorders. This special issue follows on the Special Issue in 2011, then guest-edited by Dr. Blanpied and Dr. Ehlers. We have organized this issue in four sections, and we will briefly introduce the main highlights covered in this Special Issue.

2. Early trafficking events in the secretory pathway of receptors and ion channels

Virtually all membrane constituents are formed, assembled, and processed in the ER. Importantly, during these early events many of the functionalities of membrane complexes is determined. For instance, in the case of synaptic receptors such as the glutamate receptor, the subunit composition, and thus the receptors' biophysical characteristics, is determined during the assembly in the ER. **Pick and Ziff** discuss the formation of the AMPA receptor complex in the ER, the regulated exit of AMPA receptors from the ER, and how the ER is controlled by synaptic activity to modulate the composition of receptor complexes at the synapse. Another group of glutamate receptors, the metabotropic glutamate receptors (mGluRs), form a functionally highly diverse group of G-protein coupled receptors that modulate excitability, synaptic transmission and plasticity. These receptors are dynamically trafficked in and out of synapses to regulate their abundance, desensitization and signaling capacity. **Suh, Chang and Roche** discuss the posttranslational modifications and interaction partners that determine the abundance and endocytosis of mGluRs at neuronal synapses. Another impressive example of long-distance trafficking in neurons is provided by the Trk family of neurotrophin receptors. **Scott-Solomon and Kuruvilla** describe how neurotrophin receptors activated in the distal axon undergo endocytosis into signaling endosomes that convey local signals promoting axon growth, but also undergo long-distance transport to the cell body and dendrites stimulating survival, growth and maturation of the neuron. Moreover, perhaps even more remarkable, initial delivery of the TrkA receptor to its correct target compartment involves a complicated trafficking itinerary whereby the receptor is first delivered to the somatodendritic compartment, and then undergoes endocytosis before it is delivered to the axonal compartment via anterograde transport. **Ribeiro, Verpoort, and de Wit** summarize the sequence of events that underlie the trafficking of another class of membrane proteins: synaptogenic adhesion molecules, and emphasize the key sorting compartments along the endosomal system that target adhesion proteins to the synapse. These processes are critical to maintain physiological surface levels of adhesion complexes at the synaptic membrane, which is exemplified by several neurodevelopmental disorder-associated mutations in adhesion molecules that were described to impair intracellular trafficking.

3. Receptor trafficking at and around the synapse

The molecular composition of neuronal synapses is actively maintained to support ongoing synaptic transmission, but can be rapidly modulated to accommodate plastic changes in synaptic efficiency. This process involve a series of highly regulated trafficking events that control export of constituents from the ER to the plasma membrane and the subsequent insertion into the synaptic membrane. **Bourke, Bowen and Kennedy** describe how the dendritic secretory pathway is organized to maintain synaptic membrane composition and highlight recently developed live-cell imaging, protein engineering and optical techniques to manipulate and study protein trafficking at high spatiotemporal resolution. For their correct targeting, AMPA receptors are accompanied by a plethora of interacting proteins along their journey from the ER to the synaptic membrane. **Jacobi and Von Engelhardt** describe how each of these AMPA receptor-interacting proteins control critical steps in the trafficking process to the synaptic membrane. AMPA receptor-interacting proteins also determine subsynaptic receptor localization by anchoring the receptor complexes in the PSD, and shape the biophysical properties of the receptor. Members of the tetraspanin family, an evolutionary conserved group of membrane proteins, have recently been implicated in synapse function and particularly AMPA

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receptor trafficking. **Murru, Moretto and Passafaro** focus on this interesting family of membrane proteins and discuss their role in the regulation of AMPA receptor trafficking in synaptic transmission and plasticity.

Once at the synapse, membrane components are spatially organized in subsynaptic domains to optimize synaptic transmission. The heterogeneous distribution of synaptic membrane proteins, most notably the subsynaptic positioning of receptors, is a critical determinant of synaptic efficiency. **Scheefhals and MacGillavry** describe how at excitatory synapses, the ionotropic AMPA and NMDAR-type glutamate receptors are spatially segregated from the mGluRs that are enriched in the perisynaptic domain, and discuss the physiological implications of these receptor patterns for synaptic transmission and plasticity. Due to rapidly evolving improvements in fluorescence imaging, most notably super-resolution microscopy, the molecular organization of synapses has been vigorously investigated. **Chamma and Thoumine** review how these efforts have shed new light on the dynamic nanoscale organization of synaptic adhesion molecules, an important class of synaptic proteins that span the synaptic cleft and instruct the differentiation and maturation of synapses. Adhesion complexes remain present in mature synapses and contribute to synaptic plasticity by organizing molecular complexes at both the pre- and postsynaptic sides. **Henderson and Dalva** focus on a key class of transsynaptic organizing adhesion molecules: the EphB and ephrin-B families, and review how these molecules can signal bi-directionally through a number of intracellular signaling pathways that are critical for synapse formation and plasticity.

4. Cytoskeletal and trafficking events during neuronal function and disease

The targeted trafficking of neuronal constituents to their correct subcellular compartments is essential for the growth and polarization of neuronal morphology. The cytoskeleton plays a central role in organizing long-range transport, but can also locally organize structure and function of subcellular compartments. At dendritic spines for instance, the actin cytoskeleton maintains the characteristic morphology of spines, and actin dynamics mediate activity-driven changes in spine morphology. **Borovac, Bosch, and Okamoto** discuss the role of actin-binding proteins in activity-dependent processes in dendritic spines, with special emphasis on how the signaling molecule CaMKII can control actin organization through its actin-binding β-subunit, and how cAMP and cGMP second messengers regulate structural plasticity of spines. While the large scaffolding protein family of ankyrins has long been known to be essential for organizing the axon initial segment and nodes of Ranvier, recent findings have implicated specific ankyrins isoforms in postsynaptic functioning. **Smith and Penzes** discuss this novel role of ankyrin proteins at synapses, particularly in the light of how ankyrins are linked to psychiatric disorders such as bipolar disorder. **Kilinc, Creson, Rojas, Aceti, Rumbaugh** focus on the synaptic protein SYNGAP1, which has been implicated in the development of several neurodevelopmental disorders such as intellectual disability, epilepsy, autism spectrum disorders and schizophrenia. Kilinc et al., describe the current understanding of the molecular and cellular functions of SYNGAP1 in brain development, and provide exciting new experimental data on how SYNGAP1 controls different aspects of behavior.

In axons, the role of actin has been investigated mostly in the context of development, where actin dynamics have long been known to support growth cone dynamics and axon branching. Recent evidence, in particular from live cell and super-resolution imaging experiments, have however drastically expanded the repertoire of functions of actin in mature axons. Previously unrecognized actin structures in mature axons, such as actin rings, trails and hotspots have now been identified as potential new regulators of axon function. **Papandréou and Leterrier** discuss the roles of the actin cytoskeleton in different compartments of the axon: the axon initial segment, the axonal shaft and at presynaptic sites. The cell biology of the cytoskeleton is also critical for understanding and hopefully promoting neuronal repair after damage. The regenerative capacity of injured axons in the mature mammalian central nervous system is generally very limited. To overcome this, attention has been largely dedicated to environmental factors limiting regrowth of regenerating axons, while the contribution of the intrinsic ability of neurons to regenerate axons is less well understood. In particular, microtubules has been shown to be a potential target for promoting nerve regeneration in several model systems. **Chen** reviews how microtubule dynamics regulate axon development and regeneration, and focuses primarily on studies in *C. Elegans*, which is a very attractive model system to study axon regeneration in the central nervous system. Opposing the biogenesis and targeted delivery of membrane components, autophagy and lysosomal-mediated degradation of existing protein complexes critically maintains homeostasis of neuronal membrane composition. **Bingol** describes in detail the regulatory mechanisms of autophagy and discusses how steps along the autophagy and lysosomal pathways are deregulated in numerous neurological disorders, and could be targeted for therapeutic interventions.

5. Conclusion

Altogether, this collection of reviews presents a comprehensive overview of the field, discussing a broad range of important new emerging topics in neuronal cell biology, ranging from the early trafficking events to the final positioning of neuronal components. Integrating expertise from different technological advances and model systems, this field will continue to develop our understanding of how membrane trafficking and cytoskeletal dynamics contribute to different aspects of neuronal functioning. Ultimately, these efforts are essential to identify key targets for therapeutic strategies aimed to reverse the pathological pathways that lead to brain disorders.

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