Seminars in Cell & Developmental Biology 27 (2014) 1–2

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Preface

1. Introduction

Fundamental capacities in animals such as motor performance, sensation, pain, emotion and cognition rely on the activity of neurons, the principal excitable cells of the nervous system. These capacities are determined by the large, complex and highly polarized morphology of neurons that allow them to generate, transmit and respond to electrochemical information in a precise spatiotemporal manner. Cell biology and development have been key to understanding nerve cell function. Through them we have achieved a rich understanding of the structure and function of the multiple domains that control neuronal activity including synapses, dendritic spines, the dendritic shaft, the cell body, the axon initial segment (AIS), the axon itself, nodes of Ranvier in myelinated fibers, and the axon terminal. The assembly, maintenance and adaptation of these neuronal domains depend on genetic programs, signaling pathways and environmental cues that impinge on the organization of the cytoskeleton and, crucially, on intracellular protein trafficking. Indeed, sequential progression of cargo through the secretory or endocytic pathways determines the availability of membrane proteins and organelles within specialized compartments.

It is widely accepted that many principles of intracellular trafficking of simpler cellular systems have been conserved in neurons. However, special features have emerged to accommodate the neuron's specialized morphological demands, and the identification of unique components and mechanisms that contribute to generate and regulate functional domains remain central questions of cellular neurobiology. In this special issue we present a timely collection of five reviews addressing some emerging, and exciting, concepts in the trafficking of synaptic proteins and organelles in specific neuronal domains, and our current understanding of the structures that regulate them.

Two articles explore the latest research in trafficking of glutamate receptors, which compose the majority of excitatory synapses. Although it has been firmly established that intracellular trafficking of glutamate receptors plays a key role in the regulation of synaptic efficacy, the identification of specific mechanisms that operate to control their availability and how they impinge on synaptic plasticity remain key issues in synaptic biology. In an article containing detailed molecular information Ladépêche et al., examine NMDA receptors (NMDARs) trafficking during synaptic maturation and plasticity, and focus on how trafficking is regulated by signaling molecules and direct interactions with other synaptic components, especially the dopaminergic system [1]. They also review how lateral mobility influences receptor availability by controlling the exchange between synaptic and extrasynaptic compartments. Hanley reviews the relevance of Ca^{2+}-permeable AMPA receptors (CP-AMPARs) for plasticity and disease, and examines how the balance of AMPARs and CP-AMPARs is regulated by trafficking mechanisms that deliver or remove Ca^{2+}-permeable or impermeable subunits [2].

Two other reviews focus on the role of secretory and endocytic organelles in axons, which are responsible for transmitting electrical stimuli and transporting soluble material, membrane and secreted factors over long distances. González and Couve examine the structure of the endoplasmic reticulum (ER) in axons and its emerging role in regulating the proteome through local synthesis, modification and transport of axonal proteins, which may complement classic mechanisms based on fast and slow axonal transport [3]. Schmieg et al., concentrate on the varied composition of signaling endosomes that carry neurotrophins (NT) and neurotrophin receptors (NTRs), their multiple internalization mechanisms, retrograde transport based on molecular motors and dependence on small GTPases of the Rab family [4]. They also focus on their contribution to the transport of additional molecules essential for neuronal signaling.

Finally, Leterrier and Dargent elegantly examine the architecture, assembly and maintenance of the AIS, and analyze its role in establishing and maintaining neuronal polarity [5]. Two fundamental functions of the AIS, those of a plasma membrane lateral diffusion barrier and an intracellular sieve are evaluated relative to the cytoskeleton and intracellular complexes that function as molecular scaffolds.

As with all novel concepts and discoveries, the neuronal cell biology discussed in the present set of reviews is still young and not devoid of controversies, which makes it all the more attractive. For example, accumulated evidence suggests that complex rules that vary according to synaptic history, rather than single motifs or cascades regulate dopamine 1 receptor-mediated NMDAR trafficking. Regarding CP-AMPARs it is still unknown whether TARPS, key accessory molecules that modify AMPA trafficking, control CP-AMPA availability through vesicular trafficking or lateral diffusion, and what are the molecular motors controlling their synaptic abundance. Understanding these mechanisms and the upstream signaling pathways that control them will contribute to further clarify the role of glutamate receptors in synaptic plasticity.

http://dx.doi.org/10.1016/j.semcdb.2014.03.024
1084-9521/

The scenario is not different for axonal organelles. To what extent the ER is a trafficking competent organelle in axons, whether ER membranes themselves are transported by fast or slow axonal transport, and if other secretory organelles such as the Golgi apparatus operate in axons are still controversial issues. Regarding signaling endosomes what is the role of multivesicular bodies in NT and NTR retrograde trafficking, and to what extent signaling endosomes constitute a heterogeneous population of organelles at different stages of maturity that determine their signaling properties remain to be established.

Finally the fine structure and dynamics of the AIS, and a functional model of the its barrier and filter capacities remain to be fully explained, as well as establishing whether the AIS is constructed from the trafficking of pre-assembled components.

Deciphering the fundamental biology of trafficking of organelles and proteins in the nervous system opens up possibilities to understand their pathological implications and their therapeutic value. In particular how the trafficking of CP-AMPAR relates to cocaine addiction and acute neuronal injury, and how the dopaminergic regulation of NMDARs may be related to schizophrenia and Parkinsons's disease constitute emerging and promising biomedical areas of research. Likewise, the association of the axonal ER to Alzheimer's disease, amyotrophic lateral sclerosis and human spastic paraplegias, and the relation of signaling endosome transport deficits in axons with a range of neurological disorders confirm that cell biology and biomedicine constitute an increasingly powerful alliance, which will also undoubtedly contribute to understand the role of the AIS in disease.

2. Conclusions

In this compilation we have put together only a handful of reviews that are representative of many additional topics in this fast expanding field. However, we hope to strengthen a unifying vision whereby physiologically relevant neuronal compartments share their dependence on the highly orchestrated and dynamic processes of intracellular trafficking. We also hope that remaining challenges and controversies, together with new technological advances, will fuel creative research in this stimulating area.

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Available online 28 March 2014