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Introduction to the Special Issue on Membrane Trafficking in Neurons

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Intracellular membrane trafficking is a fundamental process essential for various cellular functions ranging from targeting proteins or protein complexes to subcellular membrane domains, delivering essential organelles to certain compartments with high energy demand, and regulating pathways involved in signal transduction. Given that axons can extend to lengths thousands of times of the size of the cell bodies, trafficking represents a very unique challenge for neurons because of their highly polarized and elaborate architecture. Not surprisingly, trafficking defects have been implicated in a variety of neurodevelopmental and neurodegenerative disorders. In this special issue, we have asked leading experts in the field of neuronal trafficking to discuss novel insights into the mechanisms of intracellular trafficking in neurons, and how intracellular trafficking functionally impacts neuronal development, homeostasis, as well as neurodegeneration.

During embryonic brain development, neurons are generated from radial glial cells and migrate to their final location in the cortex where they extend dendrites and axons (together referred to as “neurites”) to establish the correct neuronal circuitry. The process of neurite extension requires significant expansion of the plasma membrane, as the surface area of a mature neuron can be thousands of times larger than a spherical and immature neuronal precursor cell. To achieve such increase in cell surface area, new membrane and new membrane proteins must be synthesized and delivered through the secretory pathway. Membrane vesicles are transported from the soma to sites on distal neurites where they fuse with the plasma membrane, preferentially at the growth cones. Distinct membrane carriers are specifically targeted to different membrane domains (Quiroga et al., 2017). In addition, to support the delivery of protein and lipid components necessary for neurite extension, neurons have an extensive endoplasmic reticulum (ER) network that has a surface membrane area up to ten times more than that of the plasma membrane. The rough ER is present throughout the soma and dendrites, whereas the smooth ER is abundant in the distal dendrite and axon. Smooth ER in the axon is known to be required for the localized lipid synthesis, protein translation and quality control, as well as transmembrane protein trafficking along

the secretory pathway (Luarte et al., 2017). The abundance of axonal mRNA transcripts for secreted and transmembrane proteins supports the idea that ER-dependent protein translation occurs in the axon. Many cytoplasmic proteins are also found to be locally translated in the axon. Such temporal and spatial regulation of local translation is critical for axonal growth and guidance (Costa and Willis, 2017). Finally, mitochondria undergo dynamic anterograde transport to the growth cone, where they are believed to supply ATP necessary for the assembly and dynamics of the actin cytoskeleton at the growth cone in developing neurons (Smith and Gallo, 2017).

Human brain development over the postnatal period is characterized by rapid synaptogenesis followed by a period of selective synaptic pruning. This extensive plasticity allows neurons to selectively preserve and strengthen specific functional networks. Membrane trafficking plays a key role during synapse formation and plasticity. At excitatory synapses, long term potentiation (LTP) is enhanced through elevated surface delivery of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, whereas increased AMPA receptor endocytosis is necessary for inducing long term depression (LTD) (Roth et al., 2017). Similarly, at inhibitory synapses, surface expression, internalization and degradation of Type A γ -aminobutyric acid (GABA_A) receptors, are tightly regulated, which contributes to synaptic plasticity of GABAergic synapses (Lorenz-Guertin and Jacob, 2017). A variety of ion channels, such as voltage gated sodium and potassium channels, are known to be essential for neuronal excitability. Their proper trafficking and precise localization determine excitability and circuit function, and surprising new pathways and means of regulation are being discovered to differentially distribute different channels to axon initial segments (Misonou, 2017).

Neuronal homeostasis requires efficient degradation of damaged intracellular components and dysfunctional organelles. The highly-polarized and post-mitotic nature of neurons and their longevity present very unique challenges for cellular clearance, which raises the question as to where and when such clearance events occur in neurons, and what the underlying machinery is (Jin et al., 2017). While cytosolic and short-lived proteins are predominantly degraded within the ubiquitin-proteasome system, membrane proteins and defective organelles are removed either through the endo-lysosomal system or autophagy. Late endosomes and autophagosomes exhibit net retrograde trafficking from distal axons toward the soma where lysosomal proteolytic activity mainly occurs (Kulkarni and Maday, 2017). Consistent with this idea, mature lysosomes with full activity of hydrolases are preferentially enriched in neuronal cell bodies. However, lysosomes at distal sites, including presynaptic terminals and dendritic spines, have also been reported, indicating local regulation of protein degradation (Jin et al., 2017).

Given the importance of membrane trafficking in every stage of neuronal development and homeostasis, it is not surprising that trafficking defects underlie many different types of neurological disorders. In neurodevelopmental disorders such as autism, schizophrenia and epilepsy, altered trafficking and synaptic localization of neurotransmitter receptors, such as GABA_A receptors, are often observed (Lorenz-Guertin and Jacob, 2017). Protein complexes required for endosomal trafficking, such as BLOC-1 and BORC complexes, are found to be associated with a number of neurodevelopmental disorders (Hartwig et al., 2017). Defects in

FMRP-dependent mRNA trafficking and localized protein translation are indicated in many of the phenotypes of Fragile X syndrome (Van Driesche and Martin, 2018).

Trafficking defects have also been linked to major neurodegenerative diseases. Alterations in mRNA trafficking and axonal localization were reported in spinal muscular dystrophy (SMA), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Costa and Willis, 2017). In Alzheimer's disease (AD), enlarged endosomes represent one of the earliest pathological features before the onset of plaque deposit and clinical symptoms. Aberrant accumulation of autophagic vacuoles within dystrophic neurites is also a prominent feature in AD brains. Defective trafficking in AD neurons leads to abnormally high levels of convergence between the amyloid precursor protein (APP) and its β -secretase β -site APP cleaving enzyme 1 (BACE1), resulting in increased generation of β -amyloid peptide, the main constituent of senile plaques in AD brains (Sun and Roy, 2017).

While great progress has been made in our understanding of the cellular mechanisms regulating membrane trafficking in neurons, a number of important questions remain. For example, what are the functional roles for the interactions between axonal ER and various intracellular organelles, such as synaptic vesicles? How does mitochondrial dynamics impact growth cone extension during development? How are trafficking mechanisms regulated at the level of synapses to achieve specificity in plasticity at excitatory and inhibitory synapses? Which mRNA transcripts are locally translated in the axon? Are proteins and organelles locally degraded in the axon, or does degradation only happen in the cell body? Recent advances in technologies such as super resolution imaging, single molecule imaging, and high throughput sequencing will undoubtedly accelerate new discoveries (Van Driesche and Martin, 2018), and the next decade should prove to be even more exciting than the last.

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