Seminars in Cell & Developmental Biology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Signalling endosomes in axonal transport: Travel updates on the molecular highway

Nathalie Schmieg[a,b], Guillermo Menendez[a], Giampietro Schiavo[a,b,*], Marco Terenzio[c,*]

[a] Cancer Research UK London Research Institute, 44 Lincoln's Inn Fields, London WC2A 3LY, UK
[b] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
[c] Biological Chemistry, Weizmann Institute of Science, 1 Herzl Street, Rehovot 76100, Israel

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Axonal transport
Kidins220/ARMS
Neurotrophins
p75^{NTR}
Rab GTPases
Tetanus neurotoxin
Trk receptors

ABSTRACT

Neurons are highly polarised cells. They make contact with their targets through long axons, along which a steady flux of proteins, lipids, nucleic acids and organelles is constantly maintained. This process is crucial to the development and maintenance of the nervous system, as proven by the many neurodegenerative disorders associated with defective axonal transport. Specific pools of endocytic organelles, which travel along the axon towards the cell body, have assumed a growing importance by virtue of their transported signals. These organelles, named signalling endosomes, vehicle growth factors, such as neurotrophins, and their signalling receptors all the way from the axon terminals to the neuronal cell body.

Due to the central importance of neurotrophins in neuronal development and survival, significant efforts have gone over the years into the study of long-range neutrophin trafficking and signalling. Recent evidence has pointed to a role of signalling endosomes in the axonal retrograde transport of many morphogenetic and survival factors, increasing their importance even further. In light of these findings, signalling endosomes have shown potential for integration of different growth factors signals and the ability to decode them by differential sorting in the neuronal cell body.

In this review we aim to discuss the state of the field regarding the nature and dynamics of signalling endosomes, their signalling capabilities, their energy requirements for axonal transport and last but not least, their importance in health and disease.

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Contents

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; AR, androgen receptor; BICD, Bicaudal D; BDNF, brain-derived neurotrophic factor; BMP, bone morphogenetic protein; CAV_2, Canine Adenovirus 2; CMT, Charcot–Marie–Tooth disease; CNS, central nervous system; CTB, cholera toxin B subunit; DRG, dorsal root ganglia; ERK1/2, extracellular signal-regulated kinase 1/2; GAPDH, glyceraldehyde 3 phosphate dehydrogenase; GFP, Green Fluorescent Protein; H_CT, binding fragment of tetanus toxin; HD, Huntington's disease; NGF, nerve growth factor; NT, neurotrophin; NT3, neurotrophin 3; NT4/5, neurotrophins 4/5; NTR, neurotrophin receptor; PI3K, phosphatidylinositide 3-kinase; PLCγ, phospholipase Cγ; PS1, presenilin 1; p75^{NTR}, p75 neurotrophin receptor; SBMA, spinal and bulbar muscular atrophy; SOD1, superoxide dismutase 1; TeNT, tetanus toxin; Trk, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor.

* Corresponding authors.
E-mail addresses: giampietro.schiavo@ucl.ac.uk, giampietro.schiavo@cancer.org.uk (G. Schiavo), marco.terenzio@weizmann.ac.il (M. Terenzio).

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http://dx.doi.org/10.1016/j.semcdb.2013.10.004

Please cite this article in press as: Schmieg N, et al. Signalling endosomes in axonal transport: Travel updates on the molecular highway. Semin Cell Dev Biol (2013), http://dx.doi.org/10.1016/j.semcdb.2013.10.004

1. Introduction

A major challenge for neurons is to maintain efficient communication over long distances. This process is fulfilled by long-range transport, which allows synapses located far away in the periphery to send signals back to the cell soma and vice versa. To put things in perspective, axons of motor and sensory neurons reach up to a metre in length in humans, whilst an average cell is only a few tens of micrometres long. Signals from as far as the tip of an axon need to reach the cytoplasm and/or the nucleus to regulate gene expression, whereas local signalling is required to maintain synaptic integrity and network stability. In neurons, long-range communication is achieved via transmission of electrical stimuli and by active transport of soluble complexes and membrane compartments. This process ensures correct signalling from distal synapses to the cell soma, and at the same time delivers proteins, organelles such as mitochondria and cellular components from the cell body to synapses and back [1].

Distal signalling in neurons occurs via the microtubule-dependent transport of a population of endosomes referred as signalling endosomes (Fig. 1), which is characterised by the presence of various receptor–ligand complexes, such as neurotrophin (NT) – neurotrophin receptors (NTRs), as cargoes. NTs have major roles in the central and peripheral nervous systems, such as neuronal development, survival, synaptic plasticity and nerve repair [2,3]. Their importance is emphasised by the finding that knockout mice for any of the NTs die soon after birth [4], and that deficits in their axonal transport are implicated in several neurodegenerative diseases, such as Alzheimer's disease (AD) and Huntington's disease (HD) [5]. NTs start their long-distance signals at axonal endings, influencing gene transcription via axonal retrograde transport and modulating axonal and synaptic functions mainly via local signalling [6]. They constitute therefore a great example of how elegantly neurons address the challenge of long-range vs local communication. The NT family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins 4/5 (NT4/5) and neurotrophin 3 (NT3). NTs bind with differential affinity to two families of receptors, the tropomyosin receptor kinase (Trk) family and $p75^{NTR}$. Individual NTs show preferential affinity for different Trks: NGF binds preferentially to TrkA, BDNF and NT4/5 to TrkB, and NT3 to TrkC. In contrast, all the NTs bind $p75^{NTR}$ [2].

In this review, we will summarise our current understanding of the nature of NT signalling endosomes in neurons. We will then describe the mechanisms of endocytosis, long-range transport and somatic trafficking of these organelles, their associated molecules and the emerging importance of deficits of axonal transport of signalling endosomes and other organelles in neurodegenerative diseases. We will conclude by briefly discussing the source of energy for the movement of signalling endosomes and a few examples of emerging axonal signalling molecules.

2. The signalling endosome hypothesis

Until few years ago, the textbook view of how signalling occurs was that this process is controlled by diffusion. It was widely believed that once activated, growth factor receptors would follow the classical degradative pathway, whilst controlling downstream signalling [7].

However, long-range NT signalling in neurons is hardly explainable by diffusion alone due to the sheer distance between the growth cone or the synapse and the cell body that needs to be covered by the activated receptor–ligand complexes. Active transport seems necessary, and indeed early experiments showed the requirement of the microtubule cytoskeleton [8] and cytoplasmic dynein [9–11] for NT receptor trafficking from the periphery to the cell body. Along the same lines, cytoplasmic dynein-mediated transport was shown to be necessary for NT-dependent survival signalling in sensory neurons [12].

To address the mechanism regulating this phenomenon, the "signalling endosome hypothesis" was formulated, according to which signal transmission in neurons would be accomplished by the compartmentalisation of signalling complexes and accessory factors in membrane-bound organelles, which are transported along axons in the retrograde direction towards the soma (Fig. 1) [13]. Mobley and his team compared the efficiency of ERK1/2 signalling from axonal retrograde endosomes to diffusion-based signalling. According to their study, NT signalling from axonal endosomes is more efficient over a distance between 1.3 μm and 13 μm [14]. They suggested that cells use diffusion-based mechanisms for distances below 200 nm and microtubule-dependent transport over larger distances [13]. Furthermore, they concluded that the receptor-dependent phosphorylation of downstream signalling complexes, which occurs on endosomal membranes, yields multiple cycles of phosphorylation and dephosphorylation (regenerating signal), whereas signalling phosphorylation controlled by diffusion is unidirectional and determines a single phosphorylation/dephosphorylation cycle (terminal phosphorylation) [14]. Crucially, NTR signalling plays a crucial role in the axonal transport of these organelles since pre-treatment with chemical inhibitors blocking either Trk activity or other downstream kinases, such as phosphatidylinositide 3-kinase (PI3K), cause the disruption of the dynein-dependent transport of NGF in sensory neurons [15].

It is important to stress that almost 10 years after the original hypothesis was formulated [13], the functional definition of signalling endosome is still controversial, and a general consensus regarding the nature of these organelles is lacking. In order to investigate long-range transport of signalling endosomes in neurons, a variety of probes and approaches, ranging from nanoparticles to intravital imaging assays have been developed (see Appendix A). These techniques have produced a wealth of data, which further highlights the complexity of this organelle in terms of its biological composition and signalling capabilities. In this review, we will

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