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Action in the Axon: generation and transport of signaling endosomes

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Abstract

Neurons extend axonal processes over long distances, necessitating efficient transport mechanisms to convey target-derived neurotrophic survival signals from remote distal axons to cell bodies. Retrograde transport, powered by dynein motors, supplies cell bodies with survival signals in the form of "signaling endosomes". In this review, we will discuss new advances in our understanding of the motor proteins that bind to and move signaling components in a retrograde direction, and discuss mechanisms that might specify distinct neuronal responses to spatially restricted neurotrophin signals. Disruption of retrograde transport leads to a variety of neurodegenerative diseases, highlighting the role of retrograde transport of signaling endosomes for axonal maintenance and the importance of efficient transport for neuronal survival and function.

Retrograde axonal transport mechanisms

Neurons extend long axons to contact post-synaptic targets far removed from the neuronal cell body. Hence long-range communication between the nerve ending and the cell body is essential for axonal pathfinding, target innervation, plasticity and survival. The neurotrophin family, including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin 3 or 4 (NT-3 and NT-4), are well-characterized growth factors that are often produced in post-synaptic cells and initiate signals at axon terminals by binding specific Trk receptors [1,2]. How are these signals conveyed to the cell body in order to alter gene expression? Several lines of experiments indicate that transport by microtubule-dependent dynein motors transmit these long-range signals [3–6]. Although there exist alternative models [4,7,8], it is widely accepted that vesicular-based transport of a "signaling endosome" is required for many, if not most, aspects of retrograde signaling mechanisms and will be the focus of this review.

In compartmentalized cultures of sensory and sympathetic neurons, activated phosphorylated Trks (P-Trks) accumulate in cell bodies upon distal axon exposure to neurotrophins [9–11]. The signaling endosome model proposes that upon ligand binding and activation, Trk receptors at the distal axon are internalized via clathrin-mediated [12–14] or pincher-dependent endocytosis [15,16]. The resultant vesicles containing the ligand-receptor complex are retrogradely transported to the cell body in order to mediate a survival response [3,7–11,17, 18].

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A major challenge in the field has been to define the essential components of the signaling endosome. Transport of activated receptors can occur even when minimal amounts of ligand are transported; indeed a single NGF dimer molecule is sufficient to maintain Trk activity during retrograde transport [19]. Vesicles containing neurotrophins and Trks have also been found to include activated components of the Ras-MAP kinase, PLCγ and PI3 kinase pathways [12,13,20,21]. These vesicles could therefore carry entire signaling complexes, capable of recapitulating in their entirety the signaling events that occurred at the nerve terminal [22].

It has long been thought that components of the Ras-MAP kinase, PLCγ and PI3 kinase pathways, are activated either in association with signaling endosomes or in the cell body upon arrival of the signaling endosome. In the cell body, critical kinases such as Rsks and Erk5, translocate to the nucleus, where they phosphorylate and activate transcription factors such as CREB to mediate neurotrophin-induced gene expression. However, a recent study has proposed instead that the transcription factor CREB itself is a component of the signaling endosome. Jaffrey and colleagues demonstrated that mRNA encoding CREB is located in the axon and is locally translated in response to distal axon stimulation with NGF. Since newly synthesized CREB in the axons co-localizes with both P-Trk and P-Erk immuno-reactivity, the investigators suggest that axonally synthesized CREB is transported through the axon together with the TrkA-signaling complexes [23]. The idea that transcription factors themselves might be co-transported with retrograde signaling endosomes provides enticing new possibilities for retrograde signaling.

Motor proteins and mechanisms of cargo recognition

Intracellular transport in axons relies on the microtubule-dependent motors, dyneins and kinesins, which mediate retrograde and anterograde transport respectively [24]. Thus dyneins are the motor responsible for transporting signaling endosomes [4,5,25]. While kinesins are a large gene family with 45 members, allowing a high degree of specificity with regard to expression and cargo selectivity [26], the mechanism for specificity of dyneins is much less obvious. The motor domain of cytoplasmic dynein is encoded by a single gene, *dnhc1*. This motor-domain protein associates with intermediate chains, light intermediate chains, light chains, and a dynactin complex; any of these might provide specificity for dynein interactions with the signaling endosome. The functional roles of dynein variants, defined by different intermediate chain (IC) isoforms, were investigated with regard to their specific role during retrograde signaling [27]. A recent study has indicated that IC-1B, an isoform of the intermediate chain that is specifically expressed in the nervous system [28–31], binds to and transports neuronal TrkB signaling endosomes [27]. In contrast, the highly related, ubiquitously expressed IC-2C intermediate isoform, does not. These data indicate that the intermediate chain isoforms contribute to selective retrograde transport of signaling endosomes in the nervous system.

A second mechanism for specificity of dynein interactions involves post-translational modification of the cargo. Sumoylation in axons triggers retrograde transport of the RNA-binding protein La [32]. La is anterogradely transported into axons by kinesin motors, and once in the axon, La is covalently modified by addition of small ubiquitin-like modifying polypeptides (SUMO). Sumoylated La binds exclusively to dynein allowing retrograde transport. It is interesting to consider that sumoylation, or perhaps other post-translational modifications, may likewise target signaling endosome components for retrograde transport.

Mechanisms of specificity of responses

The idea that the subcellular location of stimulation can act as a determinant of signaling specificity was addressed by Watson *et al*.. They proposed that differential use of individual MAP kinases could account for location-specific biological effects of neurotrophins [33].

Whilst neurotrophin stimulation at the cell body results in simultaneous activation of the classic Erk1/2 pathway and alternative Erk5 pathway, retrograde signaling by neurotrophin stimulation at the distal axon leads to preferential activation of Erk5 in the cell body. In this way, the location of neurotrophin stimulation could regulate differential gene expression patterns.

The recent study demonstrating that CREB is translated in the axon upon distal-axon NGF stimulation provides another possible mechanism for location-dependent specificity [23]. The authors indicate that axon-derived CREB is transported together with the signaling endosome, and is responsible for transcriptional responses that mediate NGF-dependent survival. Translation and retrograde transport of this distinct pool of axonally localized mRNAs provides a possible new mechanism by which signaling at the distal axon may selectively regulate gene expression.

While much of the initial emphasis in studies of retrograde signaling has focused on neuronal survival, transcriptional events that promote NGF-dependent axon growth, branching and target innervation of sensory neurons must also involve retrograde signaling [35]. A recent study highlighted the role of the transcription factor serum response factor (SRF) in NGF-dependent axonal outgrowth and terminal branching. Wickramasinghe and colleagues demonstrate that NGF stimulation of axon terminals regulates SRF-dependent gene expression through activation of the MEK/ERK and MAL signaling pathways. Although the sequence of events from initial NGF-Trk signaling to axonal outgrowth has not been fully elucidated, the idea that NGF might regulate axon growth through retrograde MEK/ERK and MAL signaling, demonstrates the potential for the signaling endosome to stimulate diverse cellular responses to distal axon signaling events.

The signaling endosome hypothesis also suggests a mechanism by which neurons can use sequential neurotrophin cues for long-range axon guidance. Postganglionic sympathetic neurons that express TrkA extend their axons past intermediate targets that express NT-3, such as the vasculature, but ultimately these neurons innervate NGF-expressing target organs. While both NT3 and NGF promote axonal outgrowth of these neurons, target-derived NGF is solely responsible for retrograde survival signaling [34]. Axonal NGF stimulation induces robust Trk phosphorylation in the axon together with subsequent transport of P-TrkA, P-Erk1/2 and P-Akt to the cell body; in contrast, NT-3 stimulation of axons is unable to initiate formation of signaling endosomes and so cannot support survival. Thus, in sympathetic neurons, TrkA stimulation without endocytosis is sufficient to promote axonal growth via local signaling independent of transcriptional events. However, to support transcriptional changes that promote axon growth and long-distance survival responses, stimulation plus endocytosis of TrkA is required. The differential control of TrkA internalization and consequent retrograde signaling by NT-3 and NGF provides a mechanism for axon guidance, instructing the neuron through the sequential stages of axon growth, terminal innervation and survival. In this way, signaling endosomes allow specific responses to intermediate and final target-derived factors, thereby ensuring only neurons that correctly innervate target organs survive [34].

Retrograde transport and neurodegeneration

Retrograde transport of neurotrophin signaling endosomes requires the activity of dynein and its associated protein complex dynactin. Disruption of dynein function has been shown to cause neurodegeneration in both mice and human diseases, and it has been suggested that this may reflect impaired transport of signalling endosomes. Interestingly, disruption of either retrograde or anterograde transport can block trafficking in both directions by causing a “traffic jam”, suggesting that even diseases caused by mutations in kinesins can be influenced by disruption in retrograde transport of signalling endosomes [36].

Several mutations in dynein lead to such degenerative processes. In two lines of mice, *Legs at odd angles (Loa)* and *Cramping 1 (Cra1)*, mutations in the dynein heavy chain gene cause motor neuron disease, and neurons from these mice exhibit a defect in the fast component of retrograde transport *in vitro* [37]. The *Loa* mice also exhibit an early-onset sensory neuropathy [38]. A distinct mutation in the dynein heavy chain leads to a proprioceptive sensory neuropathy in Sprawling (*Swl*) mice [38]. In humans, a mutation in the $p150^{Glued}$ subunit of the dynactin complex has been discovered in a family with a progressive lower motor neuron disease. This mutation disrupts binding of $p150^{Glued}$ to microtubules, thereby reducing the efficiency of retrograde transport [39]. Mice with mutations in $p150^{Glued}$ also develop motor neuron disease, with pathological findings of muscle atrophy, axonal swellings, disrupted intracellular trafficking, and proliferation of degradative organelles, including lysosomes and autophagosomes [40,41]. As dynein is responsible for retrograde transport of signaling endosomes, disruption of these survival signals is likely to contribute to the neuronal dysfunction observed in diverse neurodegenerative disorders.

Several of the degenerative diseases linked to faulty axonal transport show a pattern of distal axon degeneration as the primary pathology. Hereditary spastic paraplegia (HSP) exemplifies the axonal “dying back” phenomenon, in which axons are affected with a distal to proximal progression of disease. Causative mutations for various forms of HSP occur in molecular motors themselves or in other proteins that indirectly affect axonal transport [42–44]. In some cases of ALS, denervation of the neuromuscular junction is followed by loss of ventral root fibers, and finally motor neuron cell body loss, demonstrating that a disease causing early abnormalities in transport results in motor neuron pathology originating in the distal axon [45]. Axo-terminal degeneration of motor neurons also occurs in mice with mutations in the $p150^{Glued}$ subunit of dynactin, although it is unclear whether axonopathy arises from impaired retrograde transport or an alteration in protein degradation [40,41]. The juvenile ALS-associated gene ALS2, encoding the protein Alsin, seems to play a role in transport and axonal maintenance, as several lines of Alsin-deficient mice show variable defects in endosomal trafficking of growth factor and neurotrophin receptors, including epidermal growth factor (EGF), insulin-like growth factor (IGF), and BDNF receptors [46,47], and some lines of Alsin-deficient mice also show axonal degeneration of motor neurons [48,49]. The pathology of these diseases suggests that retrograde transport may play a special role in maintaining axonal health. The signals transported from the distal axon may provide a “snapshot” of the local environment of the axon, including the supply of trophic support originating from target tissues. Therefore, when retrograde transport is defective, information about the local environment does not reach the cell body. This may initiate an axon-specific degenerative program designed to remove the axon from an incorrect or inhospitable environment. Diseases caused by defective retrograde transport may thus specifically affect axonal integrity as a primary event in disease progression. Future research will need to investigate why only a subset of diseases caused by faulty transport lead to axon-specific degeneration. The common denominator among these diseases may provide clues about the factors, environmental or otherwise, that are specifically necessary for maintaining axonal health.

Conclusions and future directions

These studies highlight the importance of functional axonal transport in projection neurons with long axons. Interrupted transport of survival signals, such as signaling endosomes containing activated neurotrophin receptors, is likely to play a role in the pathogenesis of neurodegenerative disease caused by axonal transport defects. A growing body of evidence suggests that retrograde neurotrophin signaling can elicit different effects than local cell body signaling, and the specific requirement of retrograde transport for maintaining axonal integrity may be a result of this spatially distinct neurotrophin signaling program.

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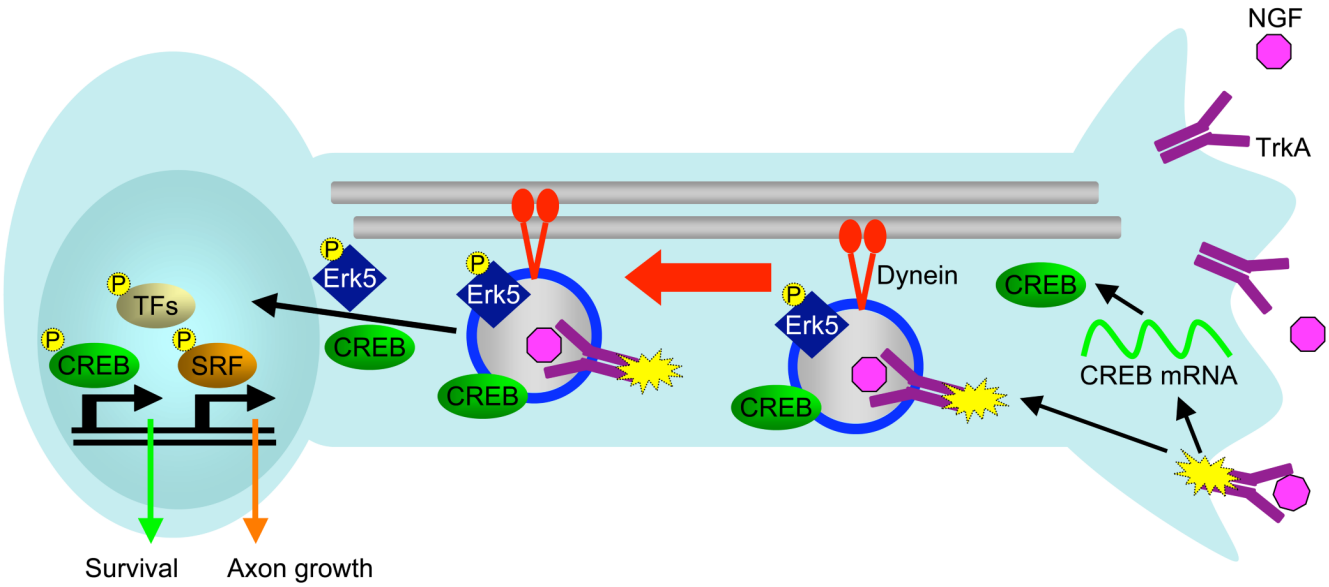

Figure 1.

Signaling endosomes are transported retrogradely from distal axons to neuronal cell bodies by the motor protein dynein along microtubules. NGF is released from target tissues, where it binds to and activates TrkA receptors at the nerve terminal. Ligand-receptor complexes are endocytosed into signaling endosomes and transported retrogradely in association with downstream signaling components. These downstream components help identify the spatial location of neurotrophin signaling events. Spatially selective signaling components include phosphorylated Erk5 and NGF-induced axonally translated CREB. Upon arrival at the cell body, translocation of signaling components to the nucleus activates a set of transcription factors to mediate target-derived NGF-dependent responses. CREB induces a set of genes necessary for survival, while SRF induces a set of genes to mediate axonal outgrowth and target innervation.

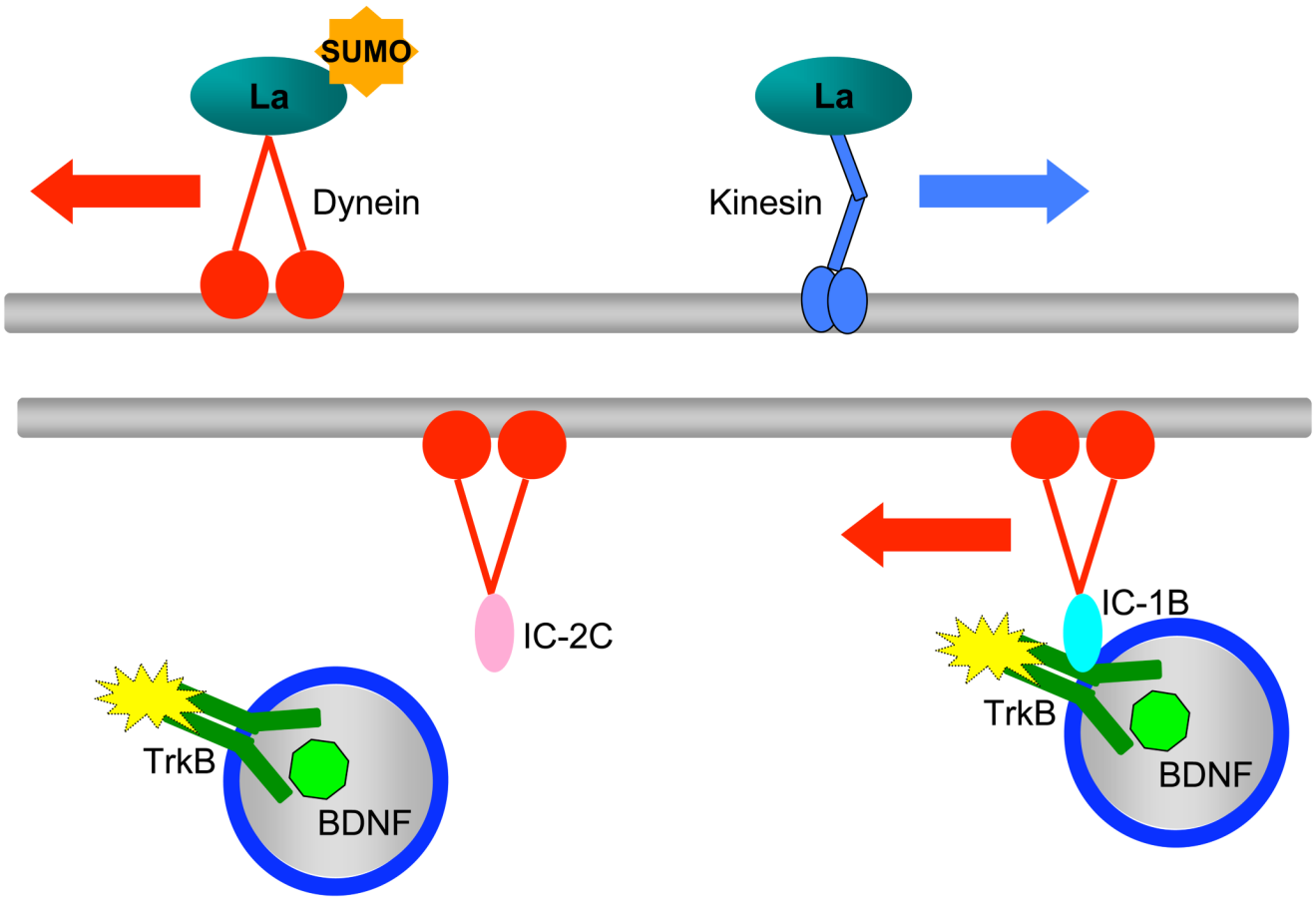

Figure 2.

Proteins are transported along the microtubules anterogradely and retrogradely by kinesins and dyneins, respectively. Post-translational modifications such as sumoylation can specify directionality of transport in the case of the RNA-binding protein La. La binds to kinesin and is anterogradely transported in the absence of sumoylation; when sumoylated, La binds to dynein and is retrogradely transported. Specificity of cargo binding for retrograde transport can be achieved through differential isoforms of dynein subunits. The neuron-specific intermediate chain IC-1B selectively binds to and transports TrkB-containing signaling endosomes, while the ubiquitously expressed IC-2C does not.