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There and back again: coordinated transcription, translation and transport in axonal survival and regeneration

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Abstract

Neurons are highly polarized cells with axonal and dendritic projections that extend over long distances. Target-derived neurotrophins provide local axonal cues that function in developing neurons, while physical or chemical injuries to long axons initiate local environmental cues in mature neurons. In both instances initial responses at the location of stimulation or injury must be coordinated with changes in the transcriptional program and subsequent changes in axonal protein content. To achieve this coordination, intracellular signals move ‘there and back again’ between axons and the nucleus. Here, we review new findings on neuronal responses to growth factors and injury and highlight the coordination of transcription, translation and transport required to mediate communication between axons and cell bodies.

Introduction

Intracellular communication is a major challenge for neurons due to the great distances traversed by long axons. Signals generated at axons in response to external stimuli must be retrogradely transported to the nucleus to elicit transcriptional changes and enable adaptations in response to the stimuli. Subsequently, new transcripts or proteins are transported back to axons from the soma to generate a multifaceted adaptive response. Thus, bidirectional transport between axon terminals and cell nuclei is an essential aspect of executing these responses. Kinesins and cytoplasmic dynein, respectively, are the molecular motors that move components along microtubules in the anterograde and retrograde direction. Disruption of axonal transport in either direction impedes responses to neurotrophins and injury, resulting in axonal degeneration and functional deterioration. For detailed information on axonal transport mechanisms, please refer to recent reviews: [1,2]. In this review, we focus on recent findings on retrograde and anterograde mechanisms

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coordinating transcription and local translation in response to neurotrophins and axonal injury.

There: retrograde signaling from axons to cell bodies

During development, neurons undergo complex changes in cellular morphology as they assemble into functional circuits. Target-derived neurotrophins (NGF, BDNF, NT3/4) initiate signaling cascades at axonal terminals by binding to their receptors (TrkA, TrkB, TrkC, p75) to regulate axonal growth and innervation, circuit refinement and survival [3]. The signaling endosome model proposes that neurotrophin binding causes activation and internalization of its receptor. The resultant vesicles are transported retrogradely via dynein motors [4,5] and elicit transcriptional changes at the soma [6–11]. Inhibition of Trk internalization and dynein-based retrograde transport reduces neuron viability [12]. Molecular characterization of signaling endosomes and how they attach to dynein remains an area of active investigation [5,13].

Axonal injuries may disrupt basal neurotrophin signaling. In addition, injury itself initiates signals conveyed from sites of injury to the nucleus to alter the transcriptional state of the neuron. Propagation of calcium waves from injury sites to the soma is a very rapid mechanism that induces transcriptional changes [14]. Additional signals initiated at the injury site are more slowly retrogradely transported to the soma by dynein to initiate additional transcriptional changes necessary for axonal regeneration after injury. While dynein is a fast motor, it moves with velocities between 1 and 3 μm/s [15]. Below, we discuss recently described mechanisms of retrograde signaling events in development and in injury responses.

Retrograde signaling during development

Initial studies identified several mRNAs that are transported to axons and are essential for axonal outgrowth, including *β-actin*. Surprisingly however, axonal mRNAs also include transcripts encoding proteins necessary for nuclear functions. Studies from Jaffrey and colleagues indicated that NGF stimulation of axon terminals results in axonal translation of the transcription factor CREB, and that newly synthesized CREB associates with NGF-TrkA signaling endosomes. Retrograde transport of phosphorylated CREB with signaling endosomes elicits transcriptional responses essential for neuronal survival [16]. As the location of NGF stimulation specifies the nature of transcriptional responses, it will be important to determine whether CREB or other transcription factors are critical for spatially distinctive responses. Notably, *Creb1* was not detected in axons of sympathetic, hippocampal or retinal neurons [17–19], suggesting that some signaling mechanisms may vary among distinct neuronal populations.

Recent studies have identified Calcineurin as a component responsible for forming signaling endosomes. Calcineurin interacts with, and dephosphorylates Dynamin1 in an NGF-dependent manner [20]. A recent study from the Kuruvilla lab indicated that formation of signaling endosomes is altered in Down syndrome due to increased expression of *RCAN1. RCAN1,* a gene triplicated in Down syndrome, encodes a Calcineurin inhibitor. Excess RCAN1 inhibited dynamin dephosphorylation and TrkA endocytosis, thereby attenuating

retrograde signaling *in vitro* and *in vivo* and leading to decreased innervation of target tissues [21] (Figure 1).

Retrograde signaling in injury response

Axonal translation also contributes to retrograde responses to injury. The demonstration that *importin β1* is translated within injured axons was initially surprising, as Importins bind nuclear localization signals (NLSs) of molecules destined for the nucleus and promote nuclear import. Following injury, locally translated Importin β1 binds Importin α, forming a functional NLS binding complex that associates with dynein. This allows nuclear factors with an NLS sequence to bind this complex and to be retrogradely transported from axons after injury. Once this cargo arrives at the soma, Importins escort the cargo through the nuclear pore, so the cargo components can elicit transcriptional changes. Blocking NLS sites on Importins leads to decreased injury response, demonstrating the importance of this communication for biological functions [22]. Fainzilber and colleagues demonstrated that only *importin β1* isoforms with a long 3′UTR are targeted to and translated within axons. Disruption of the 3′UTR axonal targeting motif greatly attenuates the majority of cell body transcriptional responses to injury and delays recovery [23].

Importin-mediated nuclear transport is regulated by a small G-protein Ran. Within the nucleus, RanGTP binds Importin β1, causing release of the cargo and nuclear export of Importin-Ran complex. Within the axons, RanBP1, along with RanGAP, catalyzes dissociation of RanGTP from the Importin complex and its hydrolysis, thereby providing access for new cargoes to bind the Importin complex. Like *importin β1*, *RanBP1* is translated in axons after injury. Together, locally translated Importin β1 and RanBP1 orchestrate the movement of critical transcription factors from axons to nuclei upon injury [24]. Although the precise axonal localization motif of *RanBP1* is not yet known, the long 3′UTR variant of *RanBP1* is required to target this mRNA to axons.

Critical cargoes transported by the Importin complex from axons to soma following injury include classical Importin cargoes such as STAT3, and non-classical Importin cargoes such as Vimentin. STAT3 is a transcription factor that is synthesized in axons following injury. Phosphorylated STAT3 (pSTAT3) is then retrogradely transported to nuclei. Together, local translation of *importin β1* and *STAT3* enables a specific signal to travel from a site of injury and initiate a proregenerative program [25,26]. Verge and colleagues identified Luman/CREB3 as another classical importin cargo that is locally synthesized in response to injury. Luman is a transmembrane transcription factor required for axonal outgrowth following injury. Local translation produces endoplasmic reticulum-associated Luman protein. Cleavage of the N-terminus of Luman enables both association with Importins and retrograde transport of the transcriptionally active protein [27]. Among the transcriptional targets regulated by Luman are several components of the Unfolded Protein Response (UPR) [28].

The non-classical importin cargo Vimentin has also been implicated in injury responses. A soluble form of Vimentin is locally synthesized and cleaved following injury, binds pErk1/2 (pErk) and thereby links pErk to importin/dynein complexes. Upon arrival at the soma, pErk

dissociates from the complex and phosphorylates and activates transcription factors such as Elk1 [29] (Figure 2).

Back again: anterograde signaling from cell body to axons

Neurotrophins or injury signals induce transcriptional changes, and the results of the new transcriptional program must be communicated back to axons to execute changes in outgrowth or axon maintenance. Transport of newly transcribed mRNAs to axons provides an efficient mechanism for this phase of communication, as multiple copies of the protein(s) can be locally synthesized in a spatially restricted fashion. Targeting of mRNAs to axons requires localization sequences, usually present in the 3′UTR, which bind specific RNA-binding proteins (RBPs). Together, mRNAs and RBPs assemble into RNA granules that are transported by kinesins to distal axons. Below, we provide examples of anterograde signaling events in development and in injury responses.

Anterograde signaling during development

ZBP1 (Zipcode binding protein1) is an RBP that interacts with *β-actin* and *GAP-43* mRNAs through zipcode and AU-rich element in their 3′UTRs, respectively, and is required for axonal localization of these transcripts [30,31]. ZBP1 has clear roles in anterograde signaling in developmental responses to target-derived neurotrophins. ZBP1 enables both nuclear export of *β-actin* mRNA, and its subsequent transport to distal axons and growth cones by kinesin [32]. ZBP1 also regulates translation of *β-actin*; following neurotrophin stimulation of distal axons, phosphorylation of ZBP1 leads to release and local translation of *β-actin* mRNA. Regulated synthesis of β-actin within distal axons allows outgrowth and turning of growth cones [30,33–35]. Together these studies identify multi-step regulation of *β-actin* mRNA by coordinated nuclear export, transport to axons, and local release and translation, which enables spatiotemporal control of axonal β-actin production and axonal navigation.

While *β-actin* is the most well characterized axonal mRNA, multiple additional transcripts are localized to developing axons and regulated by target-derived neurotrophins [36]. Neurotrophin-regulated axonal genes include *impa1,* which encodes a key enzyme in inositol cycle that produces phosphatidylinositol (PI). The long isoform mRNA, *impa1-L*, is enriched in axons and has a novel NGF-responsive sequence within the 3′UTR. Data from Riccio and colleagues suggested that local NGF activates downstream cascades to enable axonal localization and translation of *impa1*, and therefore generate PI products critical for axon maintenance [17].

Several mRNAs that are transcribed in the nucleus and translated in axons encode mitochondria-associated proteins. These include *COXIV* [37], *laminb2* and *bclw*. Axonal translation of *laminb2* can be regulated by Engrailed, NGF or BDNF. Locally synthesized LaminB2 localizes to mitochondria, and knockdown of *laminb2* leads to reduced mitochondria membrane potential and longer mitochondria. These LaminB2-dependent changes in mitochondria likely explain the critical role of LaminB2 in axon viability [38]. Work from our group demonstrated that target-derived neurotrophins also stimulate local translation of *bclw* to promote axonal viability [39].

SFPQ (splicing factor, polyglutamine rich) is an RBP that coordinates neurotrophin-stimulated anterograde axonal transport of both *bclw* and *laminb2*. Intriguingly, *bclw* and *laminb2* colocalize to the same RNA transport granules, and this colocalization requires SFPQ. Like *laminb2* and *bclw* knockdown [38,39], SFPQ knockdown results in axon degeneration [40]. Thus, SFPQ binds and coordinates expression of functionally related axonal mRNAs in space and time to enable a program of axonal survival. Future studies will determine whether co-assembly of functionally related mRNAs into transport granules represents a general phenomenon of axonal RNA regulons.

Fragile X mental retardation protein (FMRP) binds multiple distinct mRNAs, and therefore has the potential of orchestrating additional RNA regulons [41]. Two recent studies uncovered distinct roles of FMRP in axonal targeting of mRNAs. Wang et al showed that FMRP associates with both miRNAs and mRNAs. In DRG neurons, miR181-d binds and inhibits translation of its target mRNAs *map1b* and *calm1*. FMRP promotes axonal delivery of miR181-d as well as its target mRNAs, thus delivering the mRNAs in a repressed form. Local NGF stimulation induces dissociation of target mRNAs from FMRP-miR181-d, thereby terminating translational inhibition. This novel regulatory activity of FMRP is necessary for axon outgrowth [42]. Zhang et al demonstrated that FMRP binds TRF2-S, a novel RBP, and that these two RBPs have opposing effects on target mRNAs, including *rab3a* and *aplp1*. While TRF2-S promotes delivery of target mRNAs to axons and enables axon outgrowth and synaptic changes, FMRP blocks these processes [43]. In both studies, FMRP has a regulatory role in axonal growth, although this is achieved via distinct mechanisms (Figure 1).

Anterograde signaling in injury response

ZBP1 and its mRNA cargoes are also critical for axon regrowth after injury in adults. Axonal localization of *β-actin* and *GAP-43* are impaired in *ZBP1+/-* mice, and so these animals exhibit decreased regeneration after nerve injury [44]. Additional mRNAs that are localized and translated in axons upon injury include the chromatin interacting *HMGB1* and *NMP35* [45,46]. Both mRNAs require their 3′UTRs for axonal localization and contribute to axonal outgrowth after injury [45,46].

Neurons also employ epigenetic mechanisms to change gene expression for adaptation upon injury. Recently, Cavalli and colleagues demonstrated that the histone deacetylase HDAC5 has dual roles in injury responses; it functions as an epigenetic modifier regulating transcription and also functions in axons. Axonal injury induces a back-propagating calcium wave that travels to the soma. Increased intracellular Ca^{2+} activates PKCμ, leading to phosphorylation and nuclear export of HDAC5 and anterograde transport of this enzyme to the injury site. HDAC5 deacetylates axonal tubulin, reducing microtubule stability and thereby enhancing regeneration. Simultaneously, nuclear export of HDAC5 enhances acetylation of Histone H3, and thereby alters transcription [14,47] (Figure 2).

Conclusions

Recent studies reveal a multi-step coordination of transcription, local translation and transport that enable multifaceted outcomes in response to neurotrophins and injury. Local

translation in axons is a key component that functions both to initiate retrograde signaling and also to implement axonal events in response to these environmental cues. Locally synthesized transcription factors are retrogradely transported to initiate rapid and distinct transcriptional responses at the soma. To implement subsequent changes in axonal composition, several RBPs, including FMRP, ZBP1 and SFPQ, bind elements within the 3′UTR of target mRNAs and coordinate multiple steps of mRNA transport and regulation.

To date, much of the research relies on studies of cultured neurons. New techniques such as Translating Ribosome Affinity purification (TRAP) and RiboTag will enable *in vivo* analysis of the axonal translatome in response to injury or neurotrophic stimulation. *In vivo* studies will also provide insights into the functional significance of local translation. While local translation enables fast response at the site of stimuli and spatiotemporal control of protein synthesis, it is unknown why mRNAs of transcription factors are located to axons where they are locally translated and transported back to the cell body. Future studies will be needed to determine whether axonally synthesized transcription factors possess different modifications and properties, thus directing distinct transcriptional responses. In this way, axonally synthesized transcription factors may provide a mechanism to alert the cell body about axonal stimuli. Evidence that RNA regulons enable coherent coordination of transport and translation of functionally related mRNAs in neurons suggests that future studies will be needed to reveal more RNA regulons that orchestrate multiple mRNAs in morphologically complex neurons.

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Highlights

- Cues in the axonal microenvironment induce local and global changes in neurons.
- Bidirectional transport enables coordination of local and global changes.
- Some transcription factors are translated in the axon and transported to the soma.
- mRNAs are transported to and locally translated at axons for survival and growth.
- Individual RBPs coordinate multiple steps of mRNA transport and regulation.

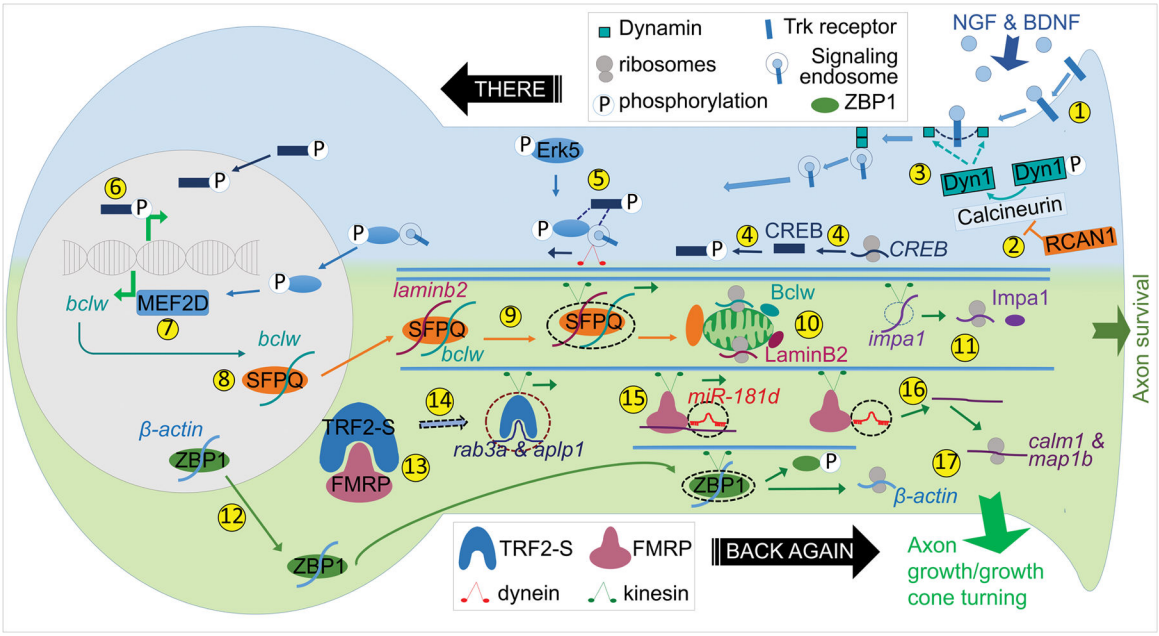

Figure 1. Anterograde and retrograde mechanisms in response to target-derived neurotrophins

(1) NGF or BDNF binds and activates Trk receptors. (2) Formation of signaling endosome is enabled by Calcineurin, which is inhibited by RCAN1. (3) Calcineurin dephosphorylates Dynamin thereby promotes endocytosis of ligand-Trk complex. (4) Neurotrophin stimulation induces local synthesis and phosphorylation of CREB, (5) which associates with retrogradely transported signaling endosome along with phosphorylated Erk5 (pErk5) and (6) activates transcriptional responses in the soma. (7) MEF2D, a downstream transcription factor of pErk5, induces *bclw* transcription. (8) SFPQ binds *bclw* for nuclear export. (9) In the soma, *laminb2* unites with SFPQ-*bclw* to be trafficked to axon via kinesin. (10) Axonal translation of *bclw* and *laminb2* at the mitochondria and (11) translation of *impa1* promote axon survival. (12) ZBP1-*β-actin* is exported from nucleus and transported via kinesin to the axon. (13) In the soma, FMRP may sequester TRF2-S, (14) which otherwise binds to *rab3a* and *aplp1* mRNAs to be transported to the axon. (15) Both *calm1* and *map1b* are anterogradely transported by FMRP-miR-181d complex via kinesin and (16) then released from this complex in the axon. Axonal TRF2-S and (17) local translation of *calm1, map1b* and *β-actin* promote axon growth and growth cone turning.

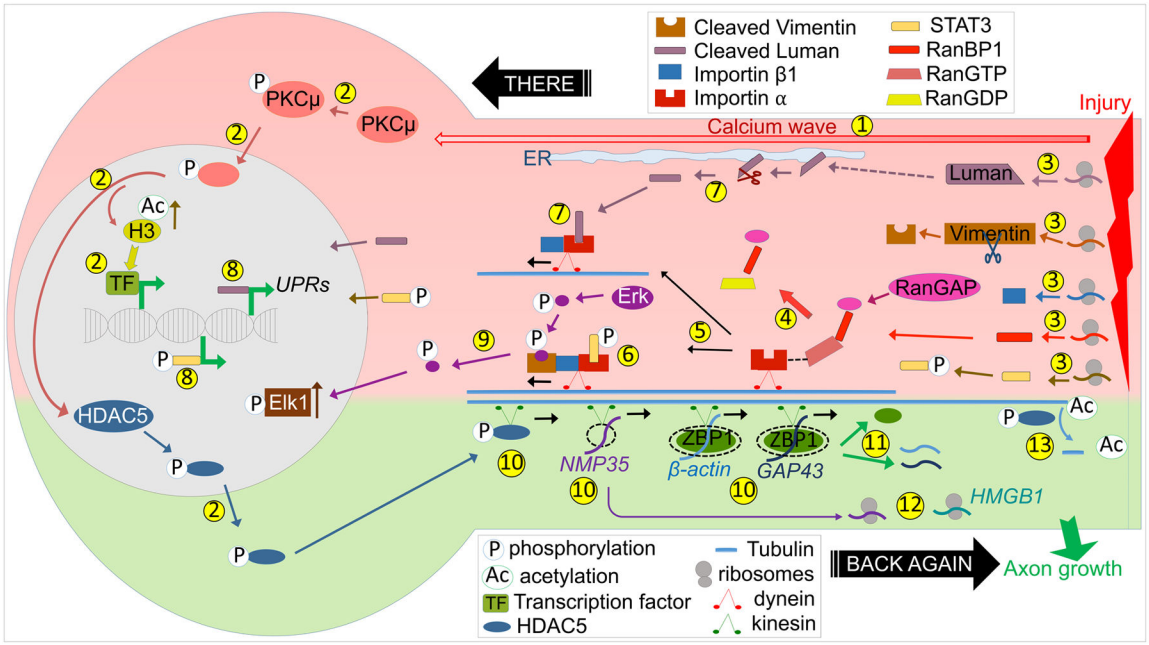

Figure 2. Anterograde and retrograde mechanisms for injury responses

(1) Injury induces back-propagating calcium wave towards the soma. (2) Ca^{+2} increase activates PKCμ and causes its nuclear translocation, which triggers HDAC5 nuclear export, increased acetylated Histone H3, and subsequent changes in transcription. (3) Injury induces local translation of *RanBP1*, *Importin β1*, *Vimentin*, *STAT3* and *Luman*. (4) RanBP1 and RanGAP trigger dissociation and hydrolysis of RanGTP. (5) This leads to formation of the importin complex by binding of Importin β1 to Importin α. (6) pSTAT3 and (7) cleaved Luman are retrogradely transported by the Importin complex via dynein, (8) and then alter transcription. (9) Cleaved Vimentin is a non-classical cargo that enables transport of pErk, which dissociates from the Importin complex and activates nuclear Elk1. (10) HDAC5, *NMP35*, and ZBP1 carrying *β-actin* or *GAP43* are delivered to axons via kinesins. (11) Release of cargo mRNAs from ZBP1, (12) local translation of *NMP35* and *HMGB1* and (13) tubulin deacetylation by HDAC5 promotes axon regrowth.