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Molecular control of local translation in axon development and maintenance

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The tips of axons are often far away from the cell soma where most proteins are synthesized. Recent work has revealed that axonal mRNA transport and localised translation are key regulatory mechanisms that allow these distant outposts of the cell to respond rapidly to extrinsic factors and maintain axonal homeostasis. Here, we review recent evidence pointing to an increasingly broad role for local protein synthesis in controlling axon shape, synaptogenesis and axon survival by regulating diverse cellular processes such as vesicle trafficking, cytoskeletal remodelling and mitochondrial integrity. We further highlight current research on the regulatory mechanisms that coordinate the localization and translation of functionally linked mRNAs in axons.

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Introduction

RNA localisation and localised translation are highly conserved mechanisms that confer spatial and temporal control of protein expression. This might be especially important for highly polarized and morphologically complex cells such as neurons [1••] in which local translation enables axons and dendrites, remote subcellular compartments, to remodel their proteome precisely in response to local demand.

The core components of the translation machinery are present in developing and mature axons, and axonal protein synthesis is involved in an increasing amount of physiological and disease-related processes [2–4]. With the combined progress made in the techniques of axonal isolation and next-generation sequencing (RNA-seq), thousands of mRNAs have now been detected in axons [5–7]. The identity of these mRNAs varies between neuronal subtypes [7], axonal subdomains [8] and throughout the axonal lifetime [8,9]. Recently, a cell-type specific genome-wide analysis of the axonal translatome further revealed the dynamic nature of local translation during the establishment and maintenance of neural wiring *in vivo*, and identified subsets of axonally translated mRNAs encoding functionally linked proteins that match the temporal needs of the axon [10••]. Here we review recent advances in the role of local translation as a regulator of axonal shape and maintenance and discuss the mechanisms by which coordinated spatiotemporal translational control of specific subsets of mRNAs in axons can be achieved.

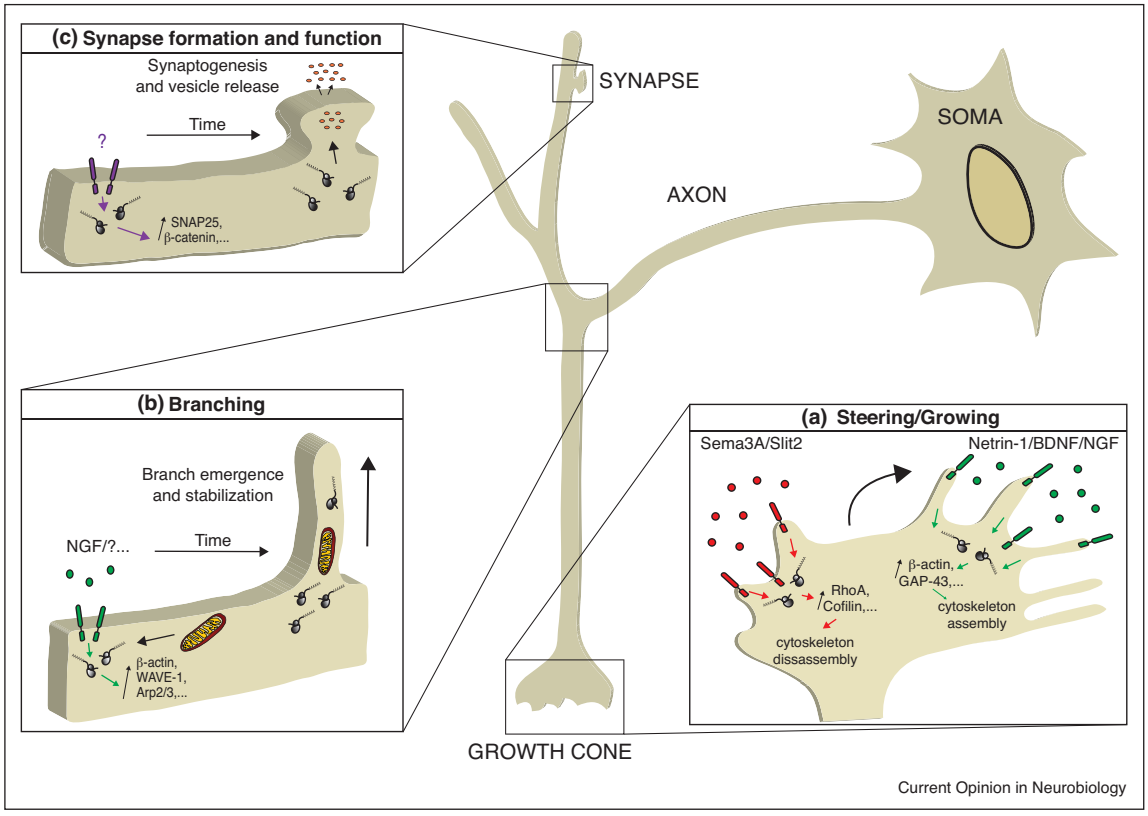
Function of axonal protein synthesis

Steering

The outgrowth and navigation of axons to the correct target area is mediated by surrounding extracellular guidance cues that are sensed by the highly motile, leading tip of the axon, the growth cone. Isolated axons separated from their cell bodies continue to grow properly when protein synthesis is acutely inhibited [11], but the cue-induced elongation or collapse response of an axon to several guidance cues is sensitive to local inhibition of translation [12]. Attractive cues such as netrin-1 and nerve growth factor (NGF) stimulate axonal protein synthesis of constituents of the cytoskeleton [13–15], whereas repulsive guidance cues like Sema3A and Slit2 induce local synthesis of proteins that promote the disassembly of the cytoskeleton [16,17]. Additionally, the asymmetrical synthesis of these proteins in growth cones exposed to a polarised cue gradient causes the local extension or withdrawal of filopodia and lamellipodia leading to steering towards or away from these *in vitro* gradients [13,14] (Figure 1a). Since these initial findings, various proteins have been shown to be locally synthesized during axon growth *in vitro* and *in vivo*, encoding cytoskeletal regulators, cell-adhesion molecules, guidance receptors and components of signaling pathways [2,10••].

Evidence demonstrating a requirement for these locally synthesized proteins for guidance *in vivo* is sparse due to the technical challenges associated with blocking protein synthesis exclusively in the axonal compartment. Studies in the mammalian spinal cord provide evidence that specific receptors (e.g. EphA2, Robo3.2) are synthesised in growing axons at the midline suggesting an underlying role for local translation in the switches of commissural growth cone responsiveness along the pathway [18,19]. *In*

Figure 1



Axonal protein synthesis in shaping the axon. **(a)** Cue-induced asymmetrical translation of mRNAs coding for cytoskeletal proteins, or their modulators, mediates growth cone responses. **(b)** Localized protein synthesis of cytoskeletal proteins mediates the emergence and stabilization of new axon branches in response to extracellular cues. **(c)** Local mRNA recruitment and translation is necessary for synaptogenesis and synapse vesicle release.

vivo inhibition of an axonally synthesised cell adhesion molecule (NFPC) [20] or an mRNA translation regulator (microRNA) [21] causes subtle defects in pathfinding and target entry in small subsets of retinal axons. This may indicate a differential reliance among retinal axonal subpopulations *in vivo* for *de novo* synthesised proteins.

Branching

Once axons have navigated to their targets, they branch to form terminal arbors bearing synapses and establish correct connections with their post-synaptic partners [23]. Translation machinery, as well as mitochondria for energy provision, is present at branching points and cue-induced local protein synthesis is required for axon branching *in vitro* [24–26] (Figure 1b). Recent dynamic imaging studies *in vivo* in Xenopus retinal ganglion cell (RGC) axon terminals demonstrated that RNA granules dock at sites that predict branch emergence and where 'hotspots' of *de novo* β-actin synthesis accumulate [22•]. Moreover, local inhibition of *β-actin* translation in axon terminals diminished both the generation and stabilization of new branches leading to reduced axonal arborisation [22•]. These results demonstrate the importance of local protein synthesis for axon branching *in vivo* [22•] and suggest a wider role in plastic (signal-induced) cell shape remodelling. The molecular mechanisms underlying the coordinated docking of specific mRNAs, translation-associated machinery and organelles at precise axonal locations are not known and are an interesting area for future study.

Synapse formation and function

Synaptogenesis also requires local protein synthesis in the pre-synaptic compartment, as highlighted by recent findings of Hengst and colleagues [27] (Figure 1c). In cultured embryonic hippocampal neurons, they show that rapid local synthesis of SNAP-25 and β-catenin occurs at sites of synapse formation and these axonally synthesized proteins are required for the assembly of presynaptic sites. Furthermore, repressing presynaptic translation affects synaptic vesicle recycling and blocking axonal translation of *SNAP-25* and *β-catenin* mRNAs impairs presynaptic vesicle release [27–29]. The relevance of these findings in the mature brain was also recently demonstrated by the finding that presynaptic local translation is needed for long-term plasticity of GABA release in established synapses [30]. Combined with the