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Maintenance mechanisms of circuit-integrated axons

Vittoria Mariano[1,2,4], Nuria Domínguez-Iturza[1,2,4], Lukas J Neukomm[1,5] and Claudia Bagni[1,3,5]

Adult, circuit-integrated neurons must be maintained and supported for the life span of their host. The attenuation of either maintenance or plasticity leads to impaired circuit function and ultimately to neurodegenerative disorders. Over the last few years, significant discoveries of molecular mechanisms were made that mediate the formation and maintenance of axons. Here, we highlight intrinsic and extrinsic mechanisms that ensure the health and survival of axons. We also briefly discuss examples of mutations associated with impaired axonal maintenance identified in specific neurological conditions. A better understanding of these mechanisms will therefore help to define targets for therapeutic interventions.

Addresses
[1] Department of Fundamental Neurosciences, University of Lausanne, Switzerland
[2] Department of Neurosciences KU Leuven, VIB Center for Brain and Disease Research, Leuven, Belgium
[3] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy

Corresponding authors: Neukomm, Lukas J (lukas.neukomm@unil.ch), Bagni, Claudia (claudia.bagni@unil.ch)
[4] Shared first authors.

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Introduction

To ensure sustained circuit function the nervous system has to establish proper wiring, integrate neuronal and non-neuronal cells, and at later stages battle the rigors of aging. Neurons use their axons for direct communication with other cells with almost no delay. Remarkably, the distance between a neuron and its target cell can be in the range of meters, for example, in giraffes, blue whales, and humans [1,2]. Although a meter does not sound impressive, it is notable that a 1 m long axon is 20 000× longer than its 50 μm long soma, and it includes >99% of the neuronal volume (Figure 1). Furthermore, axons are highly complex, and they must remain plastic throughout life, which is essential for proper circuit performance. The maintenance of such large and elaborate structures is a major bioenergetic challenge for neurons, but it is essential since axons ensure continued circuit function.

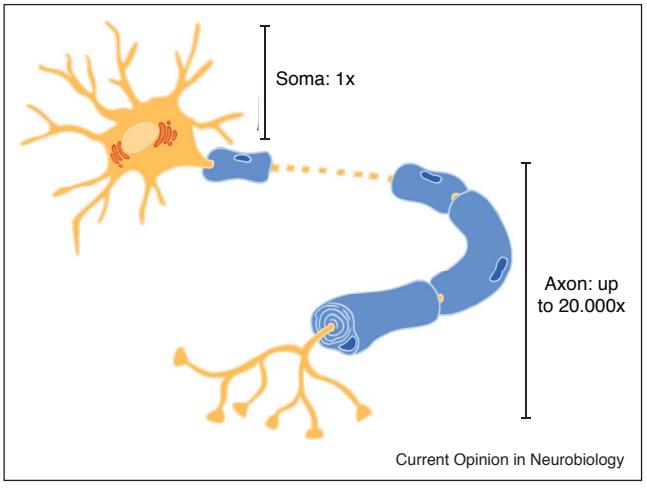
How is an axon able to rapidly and locally cope with energetic and physical challenges to ensure its survival? Recently, an accumulating body of evidence supports the idea that an adult, circuit-integrated axon cannot solely be supported by its own cell body (soma); the axon must utilize local axonal mechanisms that ensure its own autonomous survival. Besides soma-derived support mediated primarily by axonal transport, soma-independent mechanisms include: (1) intrinsic, local axonal maintenance; and (2) extrinsic glial functions to maintain axon homeostasis (Figure 2). Here, we provide an overview with some specific examples of soma-independent maintenance mechanisms that are essential for the life of the axon, and we also briefly discuss how attenuation of these mechanisms leads to neurological disorders.

Evidence of soma-independent axonal maintenance mechanisms

The soma of the neuron plays a key role in the life of the axon. A number of distinct cargos, such as RNAs, protein, vesicles and organelles, are synthesized and assembled in the soma and then transported via axonal transport out into the axon. Therefore, it is not surprising that axonal transport is crucial for the maintenance of this highly polarized structure, and defective or attenuated axonal transport culminates in axon degeneration (reviewed in [3]). There are other, distinct mechanisms that help to sustain complex axonal functions. For example, axons need to have the capability to respond quickly and locally to cues and challenges they are exposed to, without waiting for the cargo to be delivered from the soma. Such mechanisms could be of particular significance for long axons further away from their somas. There are several examples in the animal kingdom where the axon seems to be virtually autonomous and able to exist without its own soma. An unusual observation has been reported in the tiny wasp *Megaphragma*: during metamorphosis, neuronal somas are lysed, while

[5] Shared last authors.

Figure 1



The longest cell in the history of life. Axons of neurons innervating muscles in blue whales reach up to 30 m in length. For example, an axon of a 1 m long neuron can be up to 20 000× longer than its soma (around 50 μm).

axons are retained [4]. The long-term survival of anucleate axons can range from weeks to years, and this has been reported for many invertebrate phyla [5]. In *Aplysia*, after axonal injury (axotomy) the distal axon separated from the soma remains morphologically preserved for weeks rather than undergoing degeneration [6]. Similarly, in *Drosophila* mutants lacking an active axon self-destruction program, an axotomized axon remains for weeks morphologically preserved and capable of eliciting complex postsynaptic behaviors following optogenetic activation [7–9]. Taken together, these findings support the debated view of the 'autonomous axon' [10].

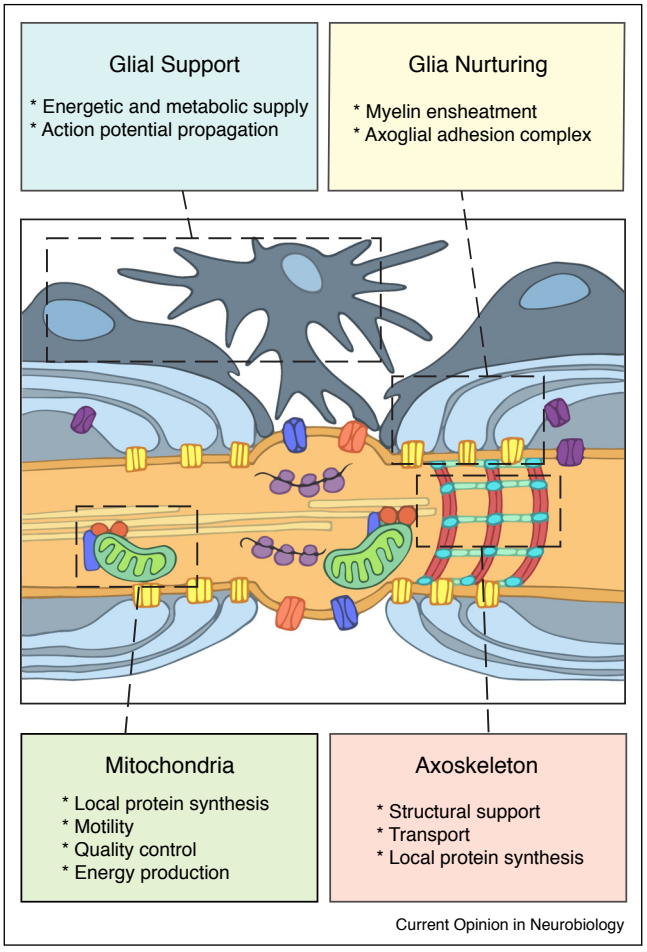
How are axons able to ensure their own survival in the absence of soma-derived support for varying amounts of time? Below, we discuss recently discovered key mechanisms that help to explain these scenarios, and we conclude with examples of diseases in which axonopathies are due to defective mechanisms of axonal survival.

Local intrinsic survival mechanisms

Axonal mitochondria

Mitostasis, the maintenance of a healthy mitochondrial population (e.g. number, quality, movement and turnover), is essential for the life of a neuron (recently reviewed in [11••]). Mitochondrial biogenesis is able to adapt in response to energy requirements of whole neurons, for example during development, and also more locally to oxidative stimuli, to electrical stimulation, or to hormones. Importantly, mitochondria are also crucial for axonal maintenance, as observed in *Caenorhabditis elegans*, where axons undergo degeneration when mitochondria are depleted [12].

Figure 2



Soma-independent axonal maintenance mechanisms. Local mechanisms allow axons to respond dynamically to environmental challenges and thereby guarantee stability. Our review focuses on four of the major soma-independent mechanisms that ensure axon maintenance and function: mitochondrial and axoskeletal support, as well as glia-derived energetic support and nurturing (green, red, blue and yellow, respectively).

Local axonal synthesis of proteins is an important mechanism for stabilizing mitochondria, and thereby the axon. In cultured embryonic *Xenopus* retinal neurons, Lamin B2 (LB2) is normally associated with nuclear membranes, however, when triggered by guidance cues, *lb2* mRNA is also transported into axons where it is locally translated and incorporated into mitochondria [13••]. This is a remarkable example of axonal protein synthesis sustaining mitochondria and, therefore, axonal survival. By contrast, inhibition of axonal LB2 synthesis results in axon degeneration. The anti-apoptotic protein Bclw is also locally translated in axons. Its synthesis prevents the disruption of mitochondria, which in turn ensures axonal health in rat and mouse sensory neurons [14]. Thus, local axonal translation of proteins that strengthen