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A glycolytic shift in Schwann cells supports injured axons

Elisabetta Babetto[1,2], Keit Men Wong[1,4] and Bogdan Beirowski[1,3] ✉

Axon degeneration is a hallmark of many neurodegenerative disorders. The current assumption is that the decision of injured axons to degenerate is cell-autonomously regulated. Here we show that Schwann cells (SCs), the glia of the peripheral nervous system, protect injured axons by virtue of a dramatic glycolytic upregulation that arises in SCs as an inherent adaptation to axon injury. This glycolytic response, paired with enhanced axon–glia metabolic coupling, supports the survival of axons. The glycolytic shift in SCs is largely driven by the metabolic signaling hub, mammalian target of rapamycin complex 1, and the downstream transcription factors hypoxia-inducible factor 1-alpha and c-Myc, which together promote glycolytic gene expression. The manipulation of glial glycolytic activity through this pathway enabled us to accelerate or delay the degeneration of perturbed axons in acute and subacute rodent axon degeneration models. Thus, we demonstrate a non-cell-autonomous metabolic mechanism that controls the fate of injured axons.

Axon degeneration plays a key etiological role in many neurodegenerative diseases[1–3]. Therefore, the preservation of axons is an important therapeutic target. This requires a mechanistic understanding of factors that regulate the stability of injured axons.

Research using experimental axon transection models over the last years has shown that axonal degeneration is regulated by a conserved program of subcellular self-destruction[1–3]. The execution of this program in injured axons involves the activation of a complex signaling cascade and the local depletion of the bioenergetic cofactor NAD^+; this culminates in a fatal energetic collapse of axons followed by structural axon disintegration[4–8]. Interventions that elevate NAD^+ or ATP concentrations in injured axons confer axon protection[4,8–13]. These discoveries point to intriguing links between a central prodegenerative program and cellular energy metabolism.

Despite these advances in our understanding of injury-induced axon death, we know surprisingly little about potential extrinsic regulators of the axonal degeneration cascade. A reductionist approach in the field studying isolated neurons has probably contributed to this void of knowledge. However, especially SCs, the glia that form a symbiotic relationship with the axons they ensheath, are known to mount dynamic responses shortly after axonal injury, long before axonal disintegration occurs[14–16]. This raises the possibility that, on axonal injury, SCs regulate the resistance of axons to degeneration. Notably, SCs have well-documented, crucial roles in other nerve injury-related aspects of axonal biology such as axonal growth and guidance[17,18]. Similarly, essential for efficient axonal regeneration, more recent studies indicate an important function of SCs for the rapid clearance of axon and myelin debris after injury through glial actin dynamics and autophagy, respectively[19–21]. Importantly, emerging evidence suggests that axon-flanking glia including SCs are metabolically coupled to axons and may provide energy-rich substrates to regulate axonal bioenergetics and integrity in different situations[22–25]. How such glial functions relate to the potential of axons to cope with stress and injury is unknown.

In this study, we investigated a role of SC energy metabolism for regulating the survival of injured axons. We show that SCs intrinsically promote the survival of axons through a dynamic glycolytic shift, a protective glial adaptation to axon injury that is driven by mammalian target of rapamycin complex 1 (mTORC1) and downstream hypoxia-inducible factor 1-alpha (Hif1α)/c-Myc signaling in SCs. The suppression of this metabolic switch in SCs through inactivation of glycolytic components or by the inhibition of the upstream mTORC1–Hif1α–c-Myc axis speeds the breakdown of injured axons. In contrast, preemptive amplification of the metabolic injury response through mTORC1 upregulation in SCs confers axonal protection after nerve injury and ameliorates the neurodegenerative phenotype in an axonopathy disease model. These discoveries unveil a central metabolic function of SCs for the support of injured axons and open new therapeutic avenues to combat axonal degeneration in disease.

Results

SCs protect injured axons. To explore a non-cell-autonomous role of SCs for the regulation of axon death, we used an in vitro model of traumatic axonal degeneration, where the degeneration of radially grown axons can be reliably quantified in the presence or absence of SCs[26] (Fig. 1a). To minimize glial effects on axonal growth that could cell-autonomously affect the rate of axonal degeneration, we first cultured embryonic dorsal root ganglion (DRG) neurons for 6 d to allow extension of long axons in the absence of glia. We then added purified SCs and used established pharmacological methods to induce axon–glia association before mechanical axonal transection. Control neuron cultures were treated equivalently but SCs were withheld. The presence of SCs robustly delayed the fragmentation of transected axons as judged by axonal cytoskeleton immunostaining (Fig. 1b,c). To test for axonal protection when SCs are restricted to contact injured axons only, we performed similar experiments using compartmentalized microfluidic devices, which allowed us to seed SCs only on axons (Fig. 1d). We found that SCs afford robust

[1]Hunter James Kelly Research Institute, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA. [2]Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA. [3]Department of Biochemistry, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA. [4]Present address: Department of Pediatrics and Adolescent Medicine, Division of Pediatric Neurology, University Medical Center Göttingen, Göttingen, Germany. ✉e-mail: bogdanbe@buffalo.edu