A new energy frontier for regeneration: non-mitochondrial pathways fuelling injury-induced axonal regrowth

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Keywords

Axonal regeneration, Central Nervous System, Metabolism, Glycolysis, Mitochondria, Pentose phosphate pathway

Abbreviations

CNS	Central nervous system
PNS	Peripheral nervous system
RGC	Retinal ganglion cell
PPP	Pentose phosphate pathway
ONC	Optic nerve crush
FAT	Fast axonal transport
DRG	Dorsal root ganglia

Summary

The ability of the mammalian central nervous system (CNS) to regenerate its damaged axons is limited, in part because of its inability to muster the required energy production machinery to the axon to support the regrowth. While mitochondria have long been considered the primary source of metabolic support, recent research has expanded the focus to include glycolysis and the pentose phosphate pathway, both of which contribute to local energy production and redox balance during regeneration. This review summarizes current advances in our understanding of these metabolic processes and integrates them into a conceptual framework that may inform further research and the development of strategies to enhance axon regeneration in the adult CNS.

Introduction

Injuries to the brain and spinal cord frequently result in irreversible damage, primarily due to the limited regenerative capacity of the adult mammalian central nervous system (CNS)[1,2]. Following injury, neurons often die, and the survivors are typically unable to regrow their axons. Neuron-extrinsic factors, such as glial scarring and the binding to the axon of growth-inhibitory molecules

and myelin debris released after injury, represent a major barrier to regeneration[1,2]. Even if these are mitigated via a beneficial, transient inflammatory response[3], adult CNS neurons still exhibit limited intrinsic growth potential, largely due to the developmental decline in the expression of regeneration-associated genes[4–6]. Despite considerable progress in understanding the barriers to regeneration and developing approaches to overcome them, current preclinical strategies fall short of achieving full circuit repair and functional recovery. The limited efficacy and frequently invasive nature of these interventions further challenge their potential for clinical translation.

Unlike mammals, invertebrates and non-mammalian vertebrates possess substantial regenerative capabilities, even in adulthood. Research on *C. elegans*, planarians and *Drosophila* has uncovered essential cellular and signalling mechanisms underlying injury-induced axonal regrowth[7–9]. Despite these insights, the considerable divergence between their nervous systems and that of mammals poses challenges for translating these findings to humans. Therefore, non-mammalian vertebrates such as fish and amphibians are frequently employed as model organisms for regenerative research[10,11]. Zebrafish (*Danio rerio*) are extensively studied due to their remarkable ability to regenerate the central nervous system (CNS) even throughout adulthood, while maintaining significant genetic and cytoarchitectural similarities with humans[10–12].

In mammals, although the CNS lacks the ability to regenerate, neurons of the peripheral nervous system (PNS) retain a degree of regenerative capacity into adulthood. This is partly because the inhibitory environment is less severe in the PNS, and partly because the neurons can reactivate regeneration-associated transcriptional programs[5,6]. The most studied neuron type are dorsal root ganglia (DRG), pseudo-unipolar sensory neurons located on the dorsal root of spinal nerves. DRG neurons possess a peripheral branch, which can regenerate, and a central branch which cannot[13,14]. Interestingly, a preconditioning lesion of the peripheral branch can activate regenerative programs that enable regrowth of the CNS branch [5,15,16], and therefore DRG neurons are extensively studied as a model for translation toward CNS repair as well. Regarding the CNS, the most common vertebrate model systems for the study of axonal regeneration are the spinal cord and the eye-to-brain pathway[1,10,17]. In mammals, the first involves the injury of, among others, corticospinal neurons. These have somata residing in the cortex and axons descending through the brainstem and spinal cord, forming the corticospinal tract, which, together with lower motor neurons, controls the voluntary movement of skeletal muscles.

The retinofugal system, referring to the tracts connecting the retina to the brain, offers a unique set of advantages to study axonal regeneration [1,10]. Although located outside of the cranium, the retina is part of the CNS. Retinal ganglion cells (RGCs) are the sole retinal neuron type whose axons project information from the eye to the brain via the optic nerve and tract. Their main targets are the optic tectum in fish and the superior colliculus along with the visual nuclei of the thalamus in mammals[18,19]. Additionally, the cytoarchitecture and physiology of the retina is extremely conserved throughout the vertebrate lineage. The leading injury model used in this system is the optic nerve crush (ONC)[10,20], damaging RGC axons within the optic nerve, proximal to the eye. In mice, this leads to the loss of approximately 80% of the RGCs within the first 2 weeks[21,22], with virtually no regeneration of axons observed within the optic nerve. By contrast, zebrafish are able to fully recover their vision after ONC both at larval and adult stages. In adult zebrafish, around 90% of RGCs survives the injury[22] and reinnervates the optic tectum within 2 weeks, leading to the recovery of vision[12,23,24].

The use of these animal models and systems, led to the discovery of pathways integral for axonal regrowth, such as the activation of mTOR and STAT3 via the deletion of *Pten* and *Socs3* in mice[25–

[29], the modulation of inflammatory mechanisms[30–35] and, among others, the modulation of developmentally regulated transcription factors[36–39]. These topics are covered in detail by recent, excellent reviews[1,2,40] and are not the focus of this manuscript. We will also not cover transplantation-based therapies, although these are gaining traction[41]. Instead, here we will discuss injury-induced axonal regeneration from a metabolic perspective. Recently published work, from across the evolutionary spectrum, has shed much-needed light on the bioenergetic requirements associated with axonal regrowth. In this review we set to summarize the current state-of-the-art on this topic and distil it into a cohesive framework of metabolic reprogramming underpinning axonal regeneration. A comprehensive understanding of these bioenergetic adaptations might provide new breakthrough avenues to achieve successful regeneration and functional recovery in the adult mammalian CNS.

The central role of mitochondria in injury-induced axonal regeneration

Energetic consequences of axonal injury

Axonal injury has been shown to induce a rapid increase in intracellular calcium[5,42]. As a compensatory mechanism, mitochondria promptly take up the excess Ca^{2+}, but in doing so deplete their membrane potential and undergo fission[43,44]. Mitochondrial depolarization causes oxidative stress, impairs energy production, and leads to ATP depletion in the axon. This eventually ends in axonal degeneration and often cell death[43]. In this scenario, an efficient clearance of damaged mitochondria and an influx of fresh mitochondria into the axon are critical to rapidly form a growth cone and sustain axonal regrowth.

Axonal mitochondrial transport underlies successful regrowth

Evidence from both invertebrate and vertebrate model system supports the critical role of mitochondria in axonal regeneration. In *C. elegans*, laser axotomy leads to a doubling in mitochondrial density in the axons and this was shown to lead to a robust regenerative response[45]. Interference with the mechanisms mediating mitochondrial prevented this accumulation and impaired regeneration. In the spontaneously regenerating adult zebrafish, axonal regrowth after ONC injury is preceded by a shrinkage of the dendrites and a relocation of mitochondria from the dendritic to the axonal compartment of the RGCs was observed during axonal elongation[46]. In the regeneration-competent mammalian PNS, injury leads to an increase in mitochondrial transport which sustains regrowth[47]. Besides trafficking within the axon, other mitochondrial dynamics, such as mitophagy, biogenesis, fusion and fission play important roles in axon (re)growth. These topics are already covered by excellent reviews[48,49]. Together, this evidence comprehensively suggests that the neuron must allocate its mitochondria to the axons to support axonal regrowth.

Mechanisms of mitochondrial transport in neurons

As neurons are extremely polarized cells, mitochondria must travel within the cell to reach the most remote extremities of axons and dendrites to exert their function[50]. This is mediated by dynein- and kinesin-mediated active transport on microtubules, respectively in the retrograde- and anterograde direction respectively (Fig. 1a). The KIF5 family (KIF5A, 5B and 5C) form the heterotetrametric kinesin-1 complex, which is the primary motor for mitochondrial anterograde transport. KIF1B (kinesin-3) and KLP6 (Kinesin-like protein 6) have also been shown to be involved in mitochondrial transport, complementing KIF5[50]. Mitochondria interact with the transport motors via adaptor proteins, the most prominent being the Miro/TRAK complex[49,50]. Miro is anchored to the mitochondrial outer membrane and interacts with TRAK, which in turn binds directly to the motor proteins. TRAK1 primarily binds kinesin KIF5 and most prominently mediates

transport in axons, while TRAK2 preferentially binds dynein and plays a bigger role in dendrites[51] (Fig. 1a). A second major adaptor protein is syntabulin, which directly links KIF5 to mitochondria for anterograde transport[50].

Developmental decline of mitochondrial transport in the mammalian CNS

Neuronal trafficking of mitochondria is prominent in the early developmental phases of the mammalian CNS but progressively declines during neuronal maturation. This is a product of both decreased expression of kinesin motors and increased mitochondrial anchoring at the peripheral compartments[52,53]. Studies on RGCs[54] and motor neurons[55] have shown that expression of KIF5A decreases into adulthood, leading to reduced mitochondrial transport. On top of motor expression, the adaptor protein Miro regulates the anchoring of mitochondria based on the intracellular concentration of calcium[50]. As synaptic vesicle release is characterized by spikes of high Ca^{2+} concentration, this contributes to the localization of mitochondria near synapses (Fig. 1b). In mature neurons, additional mechanisms of mitochondrial stalling become prevalent. The expression of syntaphilin increases during neuronal maturation and its docking is mediated not only by calcium[56], but also by the developmental decrease in Akt signalling, which leads to a downregulation of PAK5-mediated phosphorylation of syntaphilin and, in turn, increased anchoring[50,57] (Fig. 1b). Together, neuronal maturation, circuit formation and synaptic transmission are negatively correlated with mitochondrial transport in vitro as well as in vivo[50,52,53], where only 20-30% of the mitochondrial population was shown to be motile in adult neurons[58]. This little capacity for mitochondrial transport is not sufficient to reestablish axonal energetics after injury, and damaged CNS axons often undergo degeneration.

Remobilization of mitochondria in the mammalian CNS is critical for axonal regrowth

While baseline mitochondrial transport is limited in the adult CNS neurons, strategies aimed at remobilizing mitochondria are associated with axonal regrowth. Expression of KIF5A can rescue mitochondrial transport in mature RGCs[54] and is required to prevent degeneration after ONC[59]. Genetic deletion of *Pten* and *Socs3* has been shown to increase mitochondrial trafficking in cultured murine cortical neurons[60] and RGCs[61]. After injury, *Pten* and *Socs3* co-deleted RGCs upregulate *Armcx1*, which is a modulator of mitochondrial transport[62]. Overexpression of *Armcx1* leads to increased mitochondrial trafficking in adult RGCs and enables axonal regeneration *in vivo*[62]. Similarly, both a knock-out of syntaphilin or an upregulation of its Akt-PAK5 phosphorylation axis increased axonal regeneration in vitro as well as in vivo in the spinal cord[44,57,63]. As such, boosting of mitochondrial transport in adult CNS injury is a viable strategy to enable axonal regeneration.

Glycolysis to kickstart axonal regrowth

Strategies aimed at restoring the axonal mitochondrial phenotype, such as increasing mitochondrial transport[44,62,63] and/or fusion[64] have been successfully employed to sustain axonal regeneration. Nonetheless, axons need to first withstand the injury, in the presence of a disrupted cytosolic environment and local dysfunctional mitochondria. Any delay or impairment in the restoration of their transport or function can lead to an irreversible energy crisis, preventing the initiation of regeneration. Therefore, mitochondria-independent mechanisms might be at play after injury and could be required to initiate axonal regrowth.

The role of glycolysis in neuronal energetics

Differentiation of neuronal progenitor cells into neurons is accompanied by a shift from glycolysis to oxidative phosphorylation[65–67]. In contrast, astrocytes and oligodendrocytes preserve a glycolytic phenotype after maturation[68,69]. According to the lactate shuttle hypothesis, glycolysis

in glia produces lactate, which is secreted and taken up by neurons, which use it as a substrate to fuel oxidative phosphorylation[69,70]. While ample evidence makes this hypothesis the *de facto* model of brain energy metabolism, recent findings in both *C. elegans* and mice suggests that neurons autonomously carry out glycolysis and can regulate it at a subcellular compartment level to contribute significantly to energy production[71,72]. In vivo, evidence from mice showed that glucose uptake and glycolysis are essential for basal neuronal functions[73] and that electrical stimulation of neuronal firing induces glycolysis rather than oxidative phosphorylation, temporarily making neurons net exporters of lactate[74]. One of the aspects for which glycolysis has been shown to be critical in neurons is fast axonal transport (FAT). Long range retrograde and anterograde transport of cargo in vesicles is essential for neuronal health but requires a constant supply of ATP to occur. Striking findings showed that a blockade of mitochondrial energy production did not affect FAT, while a blockade of several steps of glycolysis did[75,76]. This is because vesicles possess an assembly of glycolytic enzymes on their surface that allows them to produce energy on-board[75–77]. The reason for this compartmentalization of metabolism is likely the short half-life of ATP and its low coefficient of diffusion[78]. It appears that high energy-consuming processes, like kinesin-mediated movement of vesicles in the axon or cytoskeletal remodelling, require tight coupling with the enzymes of glycolysis to provide local cytosolic ATP[79,80]. This growing body of evidence for the critical role of glycolysis suggest that neurons likely adapt their metabolism frequently and at a subcellular compartment level to meet both temporal and local demands.

Glycolysis as a gatekeeper of axonal growth

In the context of axonal injury, lactate shuttle from Schwann cells to peripheral axons has been shown to support axonal regeneration[81,82]. On the other hand, in the CNS, ONC studies demonstrated that injury causes demyelination and the death of local oligodendrocytes[83], and reactive astroglia primarily acquires a neurotoxic phenotype[84,85]. Thus, it is conceivable that the neuron-glia crosstalk might be altered or impaired in these conditions, and that metabolic self-reliance of the neuron might be required to survive and at least initiate regrowth. In this scenario, glycolysis could compensate for the energetic gap left by impaired oxidative phosphorylation. In the PNS of rats, sciatic nerve injury was shown to induce the upregulation of glycolysis not only in glia but within also axons, and its inhibition induced degeneration[86]. Within the CNS, recent evidence in both zebrafish and mice, suggests that glycolysis might play a crucial role in axonal regrowth. Soon after ONC, adult zebrafish RGCs exhibited a transcriptional shift towards glycolysis in vivo. Blocking glycolysis at multiple levels of the pathway impaired the axonal outgrowth of retinal explants[87]. A comparable increase in expression of rate-limiting enzymes of glycolysis, namely PFKFB3, PFKP and lactate dehydrogenase (LDH), was detected in *Pten* and *Socs3* co-deleted RGCs[61]. Furthermore, functional studies in vitro demonstrated that axonal injury leads to a rapid upregulation of glycolysis within the axon, which is required for sustained axonal regrowth, and driven by increased axonal localization of enzymes. Together, these findings suggest that an upregulation of glycolysis is an evolutionarily conserved mechanism intrinsic to axonal regrowth. This evolutionary perspective is further supported by evidence from invertebrate models. In C. elegans the enhanced axonal regeneration observed in *ogt-1* (O-GlcNAc transferase) mutants is fuelled by glycolysis and one-carbon metabolism. Although not studied in the context of axonal regrowth specifically, in a Drosophila model of ALS it has been shown that motor neurons undergo a PFK-mediated upregulation of glycolysis as a compensatory mechanism to prevent degeneration[88]. The prominent role of glycolysis though might extend beyond injury response and not only be limited to injury-induced axonal regeneration. Like mitochondria, glycolytic enzymes have been reported to localize to axons and to their growth

cone during development in both chick DRGs[79] and murine cortical neurons[80], where they supply ATP. These findings suggest that glycolysis might be an intrinsic and evolutionarily conserved mechanism supporting axonal outgrowth more broadly, and that insights from developmental systems and diverse model organisms could uncover additional strategies to promote axonal regeneration in the adult CNS.

Deciphering the complex spatiotemporal dynamics of carbon metabolism

Carbon flux through metabolic pathways is highly dynamic and regulated beyond the expression of rate-limiting enzymes, which only reflect a fraction of the regulatory complexity. Metabolic routing of glucose and precursors such as glutamine is determined by localized, time-dependent cellular demands. These pathways are modulated post-translationally via spatial allocation of enzymes and mitochondria, as well as allosteric regulation driven by the local biochemical milieu[89]. Glycolysis was already shown to play a critical role in axons rather than the soma early after injury[61], providing most of the ATP, but a similar spatial segregation could be true for other pathways as well. Over time, the metabolic focus may shift from energy generation for survival to the biosynthesis of cellular components necessary for axonal regeneration. Understanding the spatial and temporal regulation of glycolysis in this context could unveil novel therapeutic targets for CNS repair. To investigate this, the fate of precursors can be studied via mass spectrometry. In vitro, isotope-labeled precursors could be applied locally to axons in microfluidic platforms and their rate of incorporation into lipids and amino acids can be assessed through isotope tracing[90], helping to pinpoint the critical enzymatic steps that support axonal growth. Although this approach is currently constrained by the limited yield achievable in commercial microfluidic setups, advances in mass spectrometry and the recent progress in spatial metabolomics and lipidomics[91] may help to overcome these challenges and potentially allow the study of these processes in vivo.

Axonal redox state as determinant of injury outcome

Nicotinamide adenine dinucleotide (NAD^+) is a crucial factor in neuronal survival and axon integrity[92,93]. NAD^+ levels are most prominently maintained by NMNAT2, an enzyme of the NAD salvage pathway, which has recently gained much attention to counteract axonal degeneration[92,94], especially in the context of glaucoma[95,96]. Of relevance for this review, recent findings showed that in distal axons the maintenance of a high NAD^+/NADH ratio is mediated by NMNAT2, and that this is required to fuel local glycolysis for FAT[97]. With the knock-out of NMNAT2, NAD^+ supplementation was shown to sustain the redox balance and ATP production in axonal tips, rescuing transport and axon survival[97]. From an energy metabolism standpoint, NAD^+ is reduced to NADH by enzymes of the glycolytic pathway and the TCA cycle. NADH is then oxidized back into NAD^+ via oxidative phosphorylation, but when the rate of the latter is low due to mitochondrial dysfunction or hypoxia, oxidized NAD^+ can be restored in the cytosol through the reduction of pyruvate into lactate (Fig. 2a). In the context of injury-induced axonal regrowth, increased lactate production and export have been observed in regenerating RGCs of both zebrafish and mice with *Pten* and *Socs3* co-deleted mice. Moreover, the inhibition of pyruvate reduction to lactate in the axon reduced the extent of axonal outgrowth in both models. Taken together, these findings suggest that lactate production likely serves as a key mechanism for axonal survival and regrowth initiation after injury, potentially by preserving NAD^+ levels within axons (Fig. 2a).

The importance of maintaining the axonal redox state for regrowth though likely goes beyond NAD^+. Injury causes the production of reactive oxygen species (ROS) that react with proteins and

lipids of the cells causing damage and oxidative stress [98,99]. Cells present different detoxification mechanisms against ROS, including the expression of antioxidant enzymes which either break down superoxide or reduce oxidants. These include superoxide dismutase, catalase, glutathione peroxidases and thioredoxin. The latter has been shown to be essential for successful axonal regeneration of zebrafish RGCs[87] and in mediating the conditioning effect for axonal regrowth in *Xenopus*[100]. An upregulation of thioredoxin, together with some of the glutathione peroxidases, was detected in murine regeneration-competent RGCs after ONC[61,87], pointing again at another conserved mechanism underpinning axonal regrowth (Fig. 2b). The thioredoxin system reduces oxidized cysteine residues on proteins[101] but coupled with peroxiredoxin also catalyses the conversion of H_2O_2 to H_2O[102].

Most of the detoxifying mechanisms mentioned above require NADPH as an electron donor, which is generated via the pentose phosphate pathway (PPP), starting from the glycolytic intermediate glucose-6-phosphate (Fig. 2a). The first half of the PPP, also called the oxidative branch, generates NADPH and ribose sugars required for nucleotide synthesis. In cells not actively synthesizing DNA for division, such as neurons, PPP end-products are recycled back into glycolytic intermediates via the non-oxidative branch. A strong upregulation of the enzymes of the non-oxidative branch was observed in both zebrafish and *Pten* and *Socs3* co-deleted murine RGCs early after injury. As the PPP sequesters glycolytic intermediates upstream of the ATP-yielding steps of glycolysis, its activity to replenish NADPH could negatively impact the energy production of the already challenged neuron. Therefore, the observed upregulation of the non-oxidative branch of the PPP might be essential to return intermediates to glycolysis, so they can be utilized to yield ATP. This flux of carbons though the PPP is often referred as "pentose overflow," and is commonly seen in cells with high NADPH demand, such as those under oxidative stress[103].

Detoxifying and PPP enzymes are co-regulated, being target genes of the NRF2/ARE pathway. NRF2 is a transcription factor that is inactive under homeostatic conditions. In response to oxidative stress though, it activates, migrating to the nucleus and mediating the expression of genes possessing ARE regulatory regions. An upregulation of the expression of NRF2 (*Nfe2l2*) was measured after injury in both zebrafish and regeneration-competent murine RGCs. In a recent work by Kim et al., deletion of *Nfe2l2*, inhibited the regeneration potential of *Pten* and *Socs3* co-deleted corticospinal neurons[104]. Moreover, the overexpression of the related NRF3 (*Nfe2l3*) transcription factor was reported to mediate neuroprotection of RGCs after axonal injury[105], and to promote axonal regrowth in both zebrafish and mice[87,105]. Similarly to other regeneration-associated genes in mammals, the expression of NRF3 is high in RGCs during development but decreased in adult neurons[105]. Collectively, these findings highlight the role of the NRF pathway as an orchestrator of axonal regrowth.

Organellar biosynthetic hubs support axonal regeneration

Axonal regrowth necessitates sustained anabolic metabolism. An often-overlooked mechanism required for axonal (re)growth is membrane expansion, which requires the supply of phospholipids. Newly synthesized lipids within the neuronal soma are known to be transported via vesicles along the axons to the periphery to support membrane expansion[106,107]. More intriguingly, axons have been found able to autonomously synthesize lipids, including the major membrane component phosphatidylcholine[107]. Research by Yang et al. demonstrated that deletion of lipin-1 in RGCs shifts the lipid metabolism from production of storage triglycerides to production of phospholipids and this in turn induces axonal regeneration[108]. Synthesis of phospholipids begins with the production of long-chain fatty acids during *de novo* lipogenesis.

This process requires cytosolic pyruvate and/or mitochondria-derived citrate, both of which can be produced from glucose[109] (Fig. 3). Fatty acid synthase is in fact one of the major drains of NADPH in the cell and *de novo* lipogenesis is sustained by the activity of the PPP[103]. Downstream of fatty acids, phospholipid synthesis occurs at the interface between mitochondria and the endoplasmic reticulum (ER), combining long-chain fatty acids with glycerol-3-phosphate, which in turn is also a byproduct of glycolysis[106] (Fig. 3). The accumulation of ER in the growing axon as well as the maintenance of mitochondria-ER contact sites have been shown to be important for axonal regeneration[110–113]. Therefore, it is tempting to speculate that a tight coordination between mitochondrial localization in the axon, ER contact sites and glycolysis is essential for fuelling membrane expansion and that this cooperation constitutes a core mechanism underlying successful axonal regrowth.

In addition to fatty acids, the biosynthesis of cholesterol has emerged as a relevant player in axonal (re)growth. It occurs downstream of the mevalonate pathway, which converts cytosolic acetyl-CoA derived from pyruvate or citrate into farnesyl pyrophosphate (FPP)[114,115]. FPP serves as precursor for the synthesis of cholesterol, dolichols, coenzyme Q, and is used for the prenylation of Rho and Ras family proteins[114]. As for fatty acid synthesis, both the mevalonate pathway and cholesterol synthesis require NADPH as cofactor[103,114] (Fig. 3). While local cholesterol synthesis in axons has not been demonstrated, neurons can synthesize it autonomously in the soma and transport it to the distal axon[107]. Furthermore, cholesterol biosynthesis has been shown to be essential for axonal growth in vitro[116]. Following injury, zebrafish RGCs upregulate the mevalonate and cholesterol synthesis pathway during axonal extension[87,117], a mechanism downstream of the transcription factor Srebf2[117]. Notably, Srebf2 is also an evolutionarily conserved vertebrate transcription factor involved in RGC development within the retina[118].

Somewhat contradictory to the studies above is the evidence that upstream inhibition of the mevalonate pathway with statins or depletion of cholesterol from the membrane induces regeneration of mammalian CNS axons[119,120]. As cholesterol mediates the fluidity of the membrane and the organization of lipid rafts, its depletion might be needed to allow for the translocation of protein complexes required for axonal growth. This could not only be linked to cholesterol directly, as inhibitors of protein prenylation, targeting the Ras and Rho family, have also been reported to induce axonal growth[121]. In regeneration-competent murine RGCs co-deleted for *Pten* and *Socs3* the expression of genes involved in cholesterol biosynthesis is downregulated early after ONC but is recovered later during axonal elongation[61]. These contrasting findings concerning the mevalonate-cholesterol axis underscore the need for further investigation to elucidate its complex interplay during injury-induced axonal regeneration.

Conclusions

Although functional recovery after injury in the mammalian CNS remains a distant goal, significant progress has been made over the past decade. In this review we propose a metabolic reprogramming framework that we believe is essential for successful axonal regeneration. Bioenergetic mechanisms beyond mitochondria remain a relatively unexplored frontier in axon repair. Among these, glycolysis is emerging as a key driver, particularly in the acute phase after injury, when compromised mitochondrial function causes a local energy deficit. Over time, its role may transition from ATP production to supporting biosynthetic processes, as suggested by findings from both developmental and regenerative models. Tools such as carbon isotope tracing can be used to map glucose flux and uncover novel targets. In addition, the mechanisms guiding

axonal transport of glycolytic enzymes warrant further investigation, as they offer new opportunities for spatially controlled metabolic interventions.

Traditional pharmacological approaches to modulate glycolysis are limited, as most were designed to suppress it in the context of cancer. Gene therapy using viral vectors to express rate-limiting enzymes such as PFK, PFKFB3, or LDH, fused to axonal localization tags may circumvent this and allow a spatially controlled metabolic modulation. Regarding temporal control, RNA-based approaches using lipid nanoparticles[122] could allow transient, axon-targeted expression. This may be achieved by incorporating untranslated motifs recognized by the axonal transport machinery, thereby promoting local translation in the axon[123]. These proposed strategies could enhance the effects of broader and more established interventions, such as mTOR activation or the modulation of inflammatory and developmental signalling pathways. At the same time, progress is being made in restoring axonal guidance in adulthood[124], whether through regenerating native axons or transplanted ones [41], ultimately enabling target reinnervation. In conclusion, while regeneration relies on the interplay of multiple pathways, metabolic rewiring offers a novel and promising avenue toward achieving functional recovery in the adult mammalian CNS.

Acknowledgments

All authors are financially supported by KU Leuven (C14/22/074) and Research Foundation Flanders (FWO, Belgium) (G082221N).

Conflict of interests

The authors declare no competing interests exist.

Author contributions

L. Masin: Conceptualization, Funding acquisition, Visualization, Writing—original draft, A. Zhang: Conceptualization, Funding acquisition, Writing—review and editing, S. Bergmans: Conceptualization, Funding acquisition, Writing—review and editing, L. Moons: Conceptualization, Funding acquisition, Writing—review and editing.

Figure legends

Figure 1: Regulation of axonal mitochondrial transport during neuronal development and maturation

a) *In the axon of developing CNS neurons mitochondrial trafficking is high. Mitochondria are loaded on motor protein via the Mito/TRAK complex. TRAK1 preferentially binds to kinesin for anterograde transport, while TRAK2 interacts with dynein for retrograde transport.*

b) *In mature, firing neurons, mitochondria are primarily localized to regions of high energy demands, such as synapses. Here, high Ca^{2+} induces the immobilization of mitochondria via both Miro and syntaphilin-mediated anchoring. The expression of the latter increases with neuronal maturation and, in addition to calcium, its anchoring is mediated by PAK5.*

Reduction of Akt signaling in adult neurons leads to a decreased phosphorylation of syntaphilin by PAK5, which in turn increases mitochondrial anchoring.

Abbreviations: TRAK (Trafficking kinesin-binding protein), PAK5 (P21 Activated Kinase 5). With assets from BioRender.com.

Figure 2: Glycolysis and the axonal redox state determine injury outcome

a) *After injury, glycolysis constitutes a major source of ATP for the axon. This enhanced rate of glycolysis in regenerating axons might be driven by transport of glycolytic enzymes on board of vesicles, transported into the axon from the soma. Regardless of the origin, glycolysis produces pyruvate, which is converted into lactate to preserve the axonal levels of NAD^+, together with the NAD salvage pathway. Parallel to glycolysis, glucose is utilized by the oxidative branch of the pentose phosphate pathway (oxPPP) to generate NADPH. The end-products are then recycled into glycolysis via the non-oxPPP to produce further ATP.*

b) *NADPH generated by the PPP is an essential electron donor for the glutathione system, to detoxify hydrogen peroxide, and by thioredoxin system, to reduce oxidized proteins.*

Abbreviations: G6P (glucose-6-phosphate), R5P (ribose-5-phosphate), NAM (nicotinamide), NMN (nicotinamide mononucleotide), Trx (thioredoxin), TrxR (thioredoxin reductase), P (protein), GSH (glutathione), GSSG (Glutathione disulfide), ox (oxidized), red (reduced). With assets from BioRender.com.

Figure 3: Lipid biosynthesis underlies axonal extension

a) *Axonal outgrowth requires considerable membrane extension, which in turn necessitates phospholipids and cholesterol. Axons can synthetize lipids locally, starting from precursors such as citrate and glycerol-3-phosphate, derived from glycolysis and utilizing NADPH produced by the PPP. This biosynthetic chain takes place at the interface between mitochondria and the ER. Studies in teleost models demonstrate that cholesterol also plays a critical role in axonal extension, but to this date, there is no evidence that this occurs locally in the axon. Nonetheless, cholesterol synthesis is a major drain on the cellular NADPH pool and depends on the PPP for replenishment. Finally, this switch to a lipid biosynthesis state during axonal extension is likely orchestrated by the transcription factor SREBF2.*

Abbreviations: G6P (glucose-6-phosphate), R5P (ribose-5-phosphate), AcCoA (acetyl-CoA), FPP (farnesyl pyrophosphate). With assets from BioRender.com.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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