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Metabolic regulator LKB1 is crucial for Schwann cell–mediated axon maintenance

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Schwann cells (SCs) promote axonal integrity independently of myelination by poorly understood mechanisms. Current models suggest that SC metabolism is critical for this support function and that SC metabolic deficits may lead to axonal demise. The LKB1–AMP-activated protein kinase (AMPK) kinase pathway targets several downstream effectors, including mammalian target of rapamycin (mTOR), and is a key metabolic regulator implicated in metabolic diseases. We found through molecular, structural and behavioral characterization of SC-specific mutant mice that LKB1 activity is central to axon stability, whereas AMPK and mTOR in SCs are largely dispensable. The degeneration of axons in LKB1 mutants was most dramatic in unmyelinated small sensory fibers, whereas motor axons were comparatively spared. LKB1 deletion in SCs led to abnormalities in nerve energy and lipid homeostasis and to increased lactate release. The latter acts in a compensatory manner to support distressed axons. LKB1 signaling is essential for SC-mediated axon support, a function that may be dysregulated in diabetic neuropathy.

Axons are extremely long structures with high metabolic demands due to constant ion fluxes, transport of cargoes and maintenance of their large cell-membrane surface area. It is increasingly realized that axonal integrity depends not only on neuron-derived provisions but also on support from SCs and oligodendrocytes[1,2], the enwrapping glia of the peripheral and central nervous systems (PNS and CNS), respectively. The mechanisms for this non-cell-autonomous support function remain obscure, but emerging evidence indicates that it is distinct from the glial role of insulating axons with myelin[1–3]. Metabolic substrates produced in oligodendrocytes seem to be essential for CNS axonal support[4,5], as inhibiting transport of glycolysis-derived carbohydrates (for example, pyruvate and lactate) from glia to axons results in axonal damage[5]. In accord, mitochondrial respiration in oligodendrocytes is reported to be dispensable for axon integrity, as mitochondrial disruption does not cause axonal degeneration as long as glycolytic pathways remain intact[4].

It remains unknown whether metabolic pathways in SCs may be important for axon maintenance in the PNS. Using models of SC mitochondrial dysfunction, we recently implicated abnormalities in the integrated stress response, as well as lipotoxic mechanisms, in peripheral nerve demyelination with axon loss[6]. A possible impact of aberrant SC metabolism on axon integrity was also observed in another SC mitochondrial disruption model characterized by abundant nerve demyelination and neuroinflammation[4].

While these studies attempted to shed light on glial roles in providing axon support, the metabolic control systems in enwrapping glia remain unexplored. Moreover, whether metabolic imbalances that occur in disease similarly affect axonal integrity is particularly significant given the broad association between aberrant metabolism, aging and diverse neurodegenerative conditions with axonal damage. Notably, diabetic neuropathy occurs in association with abnormal glucose and lipid metabolism. Many of the symptoms in this neuropathy result from sensory axon degeneration[7], and it has been proposed that metabolic changes in SCs are involved[8,9]. To examine the glia-axon relationship from this perspective, we sought to identify metabolic regulatory pathways in SCs that are essential for axon maintenance.

The serine/threonine kinase LKB1 (also known as Stk11) and its prime downstream target, AMPK, maintain cellular energy homeostasis by regulating key pathways of lipid, carbohydrate and protein metabolism[10,11]. LKB1 also modulates metabolism independently of AMPK by less well-characterized mechanisms, most notably via several AMPK-related kinases[12,13]. In addition to alterations of LKB1-AMPK signaling in metabolic disease and obesity, deregulation of both kinases has been implicated in neurodegeneration, including diabetic neuropathy, aging, cancer and other conditions[10,14,15]. Maintenance of energy homeostasis during cellular stress involves activation of AMPK by LKB1 or alternative upstream kinases to induce catabolism and suppress anabolic processes, to a large degree through inhibition of mTOR[16,17].

To determine whether LKB1-AMPK signaling contributes to glial support of axon integrity, we ablated LKB1 and several downstream targets, including the AMPK complex and mTOR, in SCs *in vivo*. In support of a crucial role for glial metabolic homeostasis in axon maintenance, we found that SC-specific LKB1 mutants displayed a pattern

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