COMMENTARY

A Golgi-associated lipid kinase controls peripheral nerve myelination

York Posor[a] and Volker Haucke[a,b,1]

Myelination of axons in the central nervous system and peripheral nervous system (PNS) of vertebrates including humans enables the fast, saltatory propagation of nerve impulses by restricting action potentials to short unmyelinated axonal segments termed nodes of Ranvier (1). Defects in nerve myelination are causative of a variety of myelin diseases that range from leukodystrophies to peripheral neuropathies with demyelination such as the genetically heterogenous group of Charcot-Marie Tooth (CMT) (2) disease or nonhereditary neuropathies caused by diabetes and infections. Despite the fact that the formation of myelin provides a unique secretory challenge to myelin-producing cells, we know surprisingly little about the underlying cell biological processes. In PNAS, Baba et al. (3) identify a crucial role for the Golgi-associated phosphatidylinositol 4-kinase type IIIβ (PI4KB) in the myelination of peripheral nerves by Schwann cells.

Myelin in the PNS forms as a spiral extension of the Schwann cell plasma membrane, which wraps around its target axon by lateral and radial expansion followed by compaction into the characteristic periodic layering of the myelin sheath (1). In the PNS, only axons with a diameter of 1 μm or more are myelinated, while small-diameter axons, in particular group C nerve fibers, are unmyelinated and grouped together in so-called Remak bundles. Myelinated compact axonal segments (internodes) are interspersed by nodes of Ranvier, where axonal sodium channels are concentrated (1). Previous studies have uncovered crucial cell-autonomous functions for lipids and lipid-metabolizing enzymes including phosphatidylinositol (PI) kinases and phosphatases in the regulation of myelin biogenesis (2, 4, 5).

Hence, Baba et al. (3) generated conditional knockout (cKO) mice specifically lacking PI4KB, an enzyme thought to contribute the majority of phosphatidylinositol 4-phosphate [PI(4)P]-synthesizing activity to the Golgi complex (6), in peripheral myelin-producing Schwann cells. The Golgi complex functions as a major sorting station for protein secretion to the plasma membrane but also plays important roles in protein glycosylation and the intracellular transport and modification of lipids such as cholesterol (7), a major constituent lipid of myelin (8), ceramide, and glycosphingolipids.

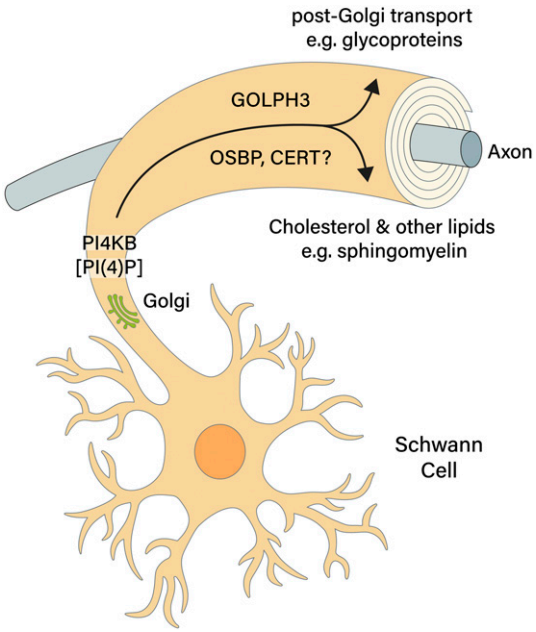

Fig. 1. Myelination of peripheral nerves and the roles of PI4KB in Schwann cell Golgi function. Formation of the myelin sheath around axons in the PNS by Schwann cells requires the lipid kinase PI4KB, a major producer of the phosphoinositide lipid PI(4)P at the Golgi complex. Local PI(4)P synthesis by PI4KB recruits effector proteins such as GOLPH3, a protein required for the localization of glycosylating enzymes to the Golgi, and the lipid transfer protein OSBP. OSBP mediates transport of the essential myelin component cholesterol from the ER to the Golgi. PI(4)P is also required for CERT-mediated transport of the sphingomyelin-precursor ceramide from the ER to the Golgi. PI4KB-deficient Schwann cells display hypomyelination and suffer from perturbed protein glycosylation and depletion of myelin-enriched lipids such as cholesterol and sphingomyelin.

[a]Department of Molecular Pharmacology and Cell Biology, Leibniz Forschungsinstitut für Molekulare Pharmakologie (FMP), 13125 Berlin, Germany; and [b]Faculty of Biology, Chemistry, Pharmacy, Freie Universität Berlin, 14195 Berlin, Germany

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[1]To whom correspondence may be addressed. Email: haucke@fmp-berlin.de.

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They found PI4KB mutant mice to be born at normal Mendelian ratios but to suffer from neurological symptoms such as hindlimb clasping, hindleg spasticity, and a subtle change of gait, e.g., behavioral abnormalities that correlated with reduced peripheral nerve conduction velocity. Further analysis using combined cell biological imaging, biochemical, and ultrastructural methods revealed a number of structural defects in sciatic nerves from mutant animals: Most prominently, large-diameter axons were hypomyelinated, whereas small-diameter axons often showed increased myelin. Nodes of Ranvier were also partially disorganized with lack of axon constriction, loss of contacts between Schwann cells and the abaxonal membrane, and reduced nodal microvilli, i.e., actin-rich cell surface protrusions that contact the axolemma. Finally, nonmyelinating Schwann cells were unable to wrap around small-diameter fibers to form proper Remak bundles in sciatic nerves from PI4KB cKO mice.

How are these defects explained at the molecular and mechanistic levels and how do they relate to PI4KB function? To address these important questions, Baba et al. (3) analyzed the subcellular distribution of PI4KB and some of the effector proteins known to bind to its lipid product PI(4)P. They found PI4KB to be concentrated at the Schwann cell perinuclear Golgi compartment and, unexpectedly and unlike other Golgi proteins, near microvilli in nodes of Ranvier. Consistent with an important role of PI4KB in Golgi function (6), they found the Golgi-localized PI(4)P-binding proteins GOLPH3 and oxysterol-binding protein (OSBP) to be mislocalized in Schwann cells from PI4KB mutant mice.

These observations correlate with and provide a rational explanation for the defects in protein glycosylation and in lipid content and composition observed in PI4KB mutant sciatic nerves (Fig. 1). The oncoprotein GOLPH3 (9) and its yeast ortholog Vps74 have been implicated in the Golgi localization of glycosylation enzymes (10). Hence, their loss in PI4KB mutant nerves likely explains the observed defects in the glycosylation pattern of so-far-unidentified sciatic nerve glycoproteins (Fig. 1). Defective protein and/or lipid glycosylation conceivably underlies at least some of the morphological defects elicited by PI4KB loss such as the reduced contacts between Schwann cells and the abaxonal membrane or the failure of nonmyelinating Schwann cells to wrap Remak bundles. A possible common denominator of these structural abnormalities are defects in cell adhesion, a process that depends on dedicated adhesion receptors (e.g., Drp2, a protein with reduced levels in PI4KB mutants) that are frequently glycosylated in the Golgi complex to enable their targeting to the correct plasma membrane domain (11).

Loss of OSBP, a lipid transfer protein that facilitates the PI(4)P-driven export of cholesterol from the endoplasmic reticulum (ER) to the Golgi complex (12), is known to result in a partial depletion of cholesterol from Golgi and post-Golgi membranes including the cell surface. Cholesterol is required for myelination on several levels. Myelin protein P_0 has been found to reside in cholesterol-rich plasma membrane domains (13), and its transport from the ER into the myelin compartment depends on cholesterol (14). Cholesterol is also a major lipid component of myelin and an important driver of nutrient signaling via the mechanistic target of rapamycin complex 1 (mTORC1), which crucially regulates both lipid biosynthesis (15) and myelination (16). Elevated signaling along the PI 3-kinase (PI3K)–Akt–mTORC1 axis, for example upon overexpression of constitutively active Akt (17) or disruption of the phosphatidylinositol 3,4,5-triphosphate [$PI(3,4,5)P_3$] 3-phosphatase PTEN (18), results in focal hypermyelination. Conversely, ablation of mTORC1 impairs myelin synthesis (16). Focal hypermyelination with myelin outfoldings downstream of hyperactive mTORC1 signaling has recently also been observed in the absence of the phosphatidylinositol 3-phosphate [PI(3)P]/phosphatidylinositol 3,5-bisphosphate [$PI(3,5)P_2$] 3-phosphatase MTMR2, its regulatory subunits MTMR5 or MTMR13, or their recruitment factor Rab35 (19).

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The data by Baba et al. confirm and extend the crucial role that signaling lipids, in particular phosphoinositides and their metabolizing enzymes (2, 19) including the plasma membrane-localized PI4KB relative PI4KA (4, 5), play in the control of myelination. They are further in line with the recently identified role of other Golgi trafficking proteins such as ADP ribosylation factor 1 and its guanine nucleotide exchange factor BIG1 in the control of myelin thickness and sorting of myelin protein P_0 in Schwann cells in the PNS (20). As always, a number of interesting questions and unsolved riddles remain. At this stage, we can only speculate about the exact molecular mechanisms that underlie the observed morphological and ultrastructural alterations observed in PI4KB cKO mice, which plausibly may relate to combined defects in lipid transport and cell adhesion mediated by myelin-associated glycoproteins (21). The nature and molecular identity of the altered glycoproteins remain unresolved. We also do not completely understand how Schwann cell-specific loss of PI4KB results in the depletion not only of cholesterol and sphingomyelin but also of other lipids, most notably phosphatidylethanolamine. One plausible explanation is that loss of PI4KB also impairs the function of other lipid transfer proteins in addition to OSBP and ceramide transfer protein (CERT), a crucial factor for ceramide shuttling to the Golgi complex (22), where it is modified to sphingomyelin and other lipids (Fig. 1). In addition to these roles of PI4KB at the Schwann cell Golgi complex in lipid and protein shuttling, it remains possible that alterations in signaling pathways important for the control of myelination [e.g., Akt, BDNF, or integrin signaling (1)] contribute to hypomyelination and the failure of Schwann cells to enwrap Remak bundles of small-diameter axons in PI4KB mutants. The unexpected localization of a subpool of PI4KB near nodal filopodia may hint at nonconventional, possibly scaffolding roles of this enzyme in Schwann cells and, possibly, other cell types. Most generally, we do not understand the mechanisms and membrane sources underlying the differential control of radial vs. longitudinal myelin membrane growth in Schwann cells. Apart from distinct signaling pathways that control internodal length [such as YAP/ Hippo signaling (23)] vs. radial membrane expansion, it is conceivable that distinct polarized vesicular trafficking routes (e.g., Golgi-derived vesicles vs. endosome-derived vesicles) fuel myelin membrane growth. Future studies will be needed to answer these exciting questions that may pave the way for the treatment of diseases related to myelin dysfunction.

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