"Axon-glia interactions and the control of myelination"

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Myelination of axons is a prerequisite for rapid impulse conduction in the nervous system and essential for normal motor and cognitive functions. In the peripheral nervous system, Schwann cells (SC) either engulf multiple small-caliber axons (Remak bundle), or single-out and spirally enwrap larger axons with a multi-lamellar myelin sheath. We have previously shown that axonal neuregulin-1 signaling to glial cells that express ErbB receptors is a critical regulator of myelination and myelin sheath thickness in vivo. Mice with reduced NRG1 gene dosage are hypomyelinated, whereas transgenic mice with elevated NRG1 expression in DRG and motoneurons are hypermyelinated. In the PNS, NRG1 type III is the responsible isoform. Whether NRG1 serves a similar function in the myelination of axons in the central nervous system is not known but of obvious clinical relevance. Also the molecular mechanisms downstream of ErbB receptor activation that initiate the spiral wrapping by SC are unknown. By targeting a null mutation of the PTEN gene to SC, we can demonstrate that the signaling lipid PtdIns(3,4,5)P3 (PIP3) induces myelin membrane outgrowth. In adult mice, elevated PIP3 activates Akt1 and causes hypermyelination as well as myelin outfoldings that resemble the pathology of human CMT4B. Surprisingly, elevated PIP3 is sufficient to induce the wrapping of small C-fiber axons in Remak bundels, and even the ensheathment of collagen fibers that completely lack axonal surface signals. These observations demonstrate a key role for PIP3 in inducing spiral wrapping and driving myelin membrane outgrowth.