This Week in The Journal

Iron Homeostasis Key to Oligodendrocyte Precursor Cell Development

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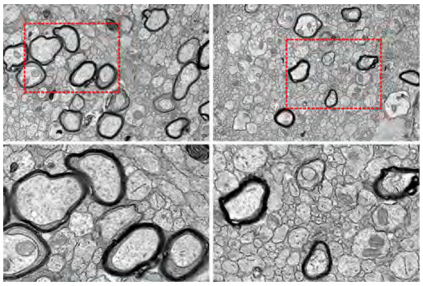
(see pages 3614–3629)

Oligodendrocyte progenitor cells (OPCs) and mature oligodendrocytes are responsible for myelinating axons, particularly during early postnatal development. Several lines of evidence point to a link between iron uptake and myelination, and iron deficiency can cause delayed myelination and OPC development. OPCs and oligodendrocytes contain more iron than any other cells in the CNS, but the role of iron handling in OPCs had not been investigated. Transferrin (Tf) is a circulating glycoprotein that binds and solubilizes iron in the blood; together they bind the transferrin receptor (Tfr) and are endocytosed to specialized endosomes. Iron is then released through a divalent metal transporter, and Tfr is recycled to the cell surface. This week, Cheli et al. show an important role for Tfr in myelination using a conditional knock-out system in developing mice specifically in OPCs, where Tfr had not been thought to act. OPCs lacking Tfr contained only half the iron of control cells and expressed significantly lower myelin proteins in addition to failing to mature properly. Postnatal deletion of Tfr from OPCs [postnatal day 2 (P2) to P7] evaluated at P15 and P30 also showed reduced iron content and myelin protein synthesis, indicative of hypomyelination. Later deletion (P30) of Tfr showed persistent hypomyelination, but mice with Tfr deletion at P60 evaluated at P90 did not differ from controls. Electron microscopy revealed fewer and thinner myelinated axons and delayed myelination at P15 and P30 in the brains of Tfr knock-out mice. Mature oligodendroglia were significantly fewer in mice lacking Tfr, but the proliferating OPC population was not affected. The authors next used RNA sequencing to examine the effects of ferritin (Fth), an intracellular iron-storage protein, and iron uptake on gene expression related to OPC development. Conditional deletion of Fth led to the upregulation of ~50 genes related to phagocytosis, whereas about 50 downregulated genes were connected to OPC development and myelination. Genes associated with iron transport and mitochondrial activity were also misregulated. Knockout of Tfr produced similar results. Together, the findings show that Tfr is essential for iron homeostasis, myelination, and development of OPCs but not for myelination or iron handling in mature oligodendrocytes.



Electron micrographs of axons from the corpus callosum of control (left) and Tfr knock-out (right) mice at P15. Scale bars: top panels, 8 μm; bottom panels, 2 μm.

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