Charcot-Marie-Tooth Disease

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Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous group of inherited disorders characterized by severe peripheral neuropathy, affecting myelinated motor and sensory axons and leading to distal muscle weakness and atrophy. Among the recessive demyelinating neuropathies (CMT4), three have been found to result from defects in enzymes of phosphoinositide metabolism. CMT4B-1 and -2 exhibit mutations in members of the myotubularin family of PI 3-phosphatases, MTMR2 and MTMR13, respectively, whereas CMT4J exhibits mutations in SAC3 (homolog of yeast FIG4), a PI(3,5)P_2 5-phosphatase (Scherer et al., 2008). A unique aspect of the MTM family is that nearly half of its members are catalytically inactive. Several of the latter have been found to play important roles in phosphoinositide homeostasis, likely by virtue of their interaction with active MTMs (Robinson et al., 2006). MTMR2, which is catalytically competent, does not display full activity unless it is complexed with the inactive MTMR13. Thus CMT4B-1 and -2 share similar pathology, with myelin outfolding in the nodal/paranodal region. Targeted alteration of the genes for MTMR2 or MTMR13 in mouse Schwann cells reproduces the demyelination found in CMT, in contrast to neuronal ablation of MTMR2, which resulted in no detectable phenotype (Scherer et al., 2008). MTMs are localized to endosomal compartments, underscoring their role in control of PI3P/PI(3,5)P_2 signaling which is important for trafficking through the endosomal system (Nicot et al., 2008). Further indication that PI3P/PI(3,5)P_2 play a crucial role in myelinating Schwann cells is provided by the discovery that CMT4J is caused by mutations in the 5-phosphatase, SAC3. The latter forms a complex with PIKfyve (a PI3P-5kinase), leading to its activation and production of PI(3,5)P_2 (Liu et al., 2010). Thus, paradoxically, loss of SAC3 (which converts

$PI(3,5)P_2$ to PI3P). leads to a decrease in $PI(3,5)P_2$. Inactivation of SAC3 in mice produces the "pale tremor mouse," characterized by both peripheral neuropathy and degeneration of the central nervous system. Although the importance of PI3P and $PI(3,5)P_2$ homeostasis has been clearly demonstrated in CMT, disorders of autophagy and a wide array of other disease states, the manner in which perturbations in this process contributes to the pathology is poorly understood, although a defect in endosomal function seems likely (McCrea & De Camilli, 2009). Compromised turnover of PI3P/$PI(3,5)P_2$ and other phosphoinositides is likely to be implicated in additional disorders as more disease genes are identified

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