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ABCA1 inhibition improves Schwann cell maturation and cholesterol deficiency in Charcot-Marie-tooth disease type 1A

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Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited peripheral neuropathy, caused by a duplication of the PMP22 gene. This leads to impaired Schwann cell function and myelin sheath formation, causing motor and sensory dysfunction in patients. Increasing evidence suggests a link between PMP22 and ATP-binding cassette transporter 1 (ABCA1), a membrane co-transporter involved in cholesterol and phospholipid efflux. Notably, Schwann cells in CMT1A exhibit reduced cholesterol levels, identifying ABCA1 as a potential therapeutic target.

In this study, we investigated the role of ABCA1 in CMT1A pathology and assessed the effect of its inhibition using PSC-833 in human and murine disease models. In the C3-PMP22 mouse model, ABCA1 gene and protein expression were significantly upregulated in sciatic nerves from 4 weeks to 1 year of age. In addition, myelin displayed reduced cholesterol levels, as demonstrated by lower lipid polarity values using the cholesterol-sensitive dye Di-4-ANEPPDHQ, as well as a general decrease in lipid content.

Similarly, increased ABCA1 gene expression was observed in Schwann cells derived from CMT1A patient iPSC (iPSC-SC) and dental pulp stem cells (DPSC-SC), as well as in C3-PMP22 primary Schwann cells. ABCA1 inhibition with PSC-833 improves Schwann cell phenotype, as indicated by increased MPZ, and decreased CJUN, PMP22, and ABCA1 expression in healthy and CMT1A DPSC-SC. Furthermore, PSC-833 increases membrane cholesterol content in giant plasma membrane vesicles from both healthy and CMT1A Schwann cells.

Finally, in vivo treatment of C3-PMP22 mice using PSC-833 improved motor function and restoration of the myelin integrity.

Together, this study underlines a consistent lipid and cholesterol deficiency in CMT1A Schwann cells, and provides evidence that ABCA1 contributes to this starvation. Inhibiting ABCA1 restores key Schwann cell functions and represents a promising therapeutic avenue for functional recovery in CMT1A.