2nd European CMT Specialists Conference
Antwerp, 23-25 October 2025

Poster P3

Lysosomal dysbalance and cargo release by Schwann cells in Charcot-Marie-Tooth disease type 1A

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Charcot-Marie-Tooth disease (CMT) is the most prevalent peripheral neuropathy, with CMT1A as the predominant subtype. CMT1A results from a duplication of the peripheral myelin protein 22 (PMP22) gene, mainly expressed in Schwann cells. While the precise mechanisms linking PMP22 overexpression to Schwann cell dysfunction remain unclear, PMP22 accumulation has been associated with lysosomes. However, its contribution to the CMT1A pathology remains unclear. We identify lysosomal abnormalities in the CMT1A C3 mouse model and validate our findings in CMT1A patient-derived Schwann cell precursors (SCP). Western blotting and immunohistochemistry demonstrated significantly increased levels of the lysosomal marker LAMP1 and enzymes Cathepsin B (CtB) and Cathepsin D (CtD) in sciatic nerves of C3 compared to wild-type (WT) mice. These results were confirmed in primary murine Schwann cells from C3 mice and human CMT1A SCP via immunocytochemistry. Transmission electron microscopy revealed increased lysosomal content and lysosomal membrane permeabilization in CMT1A Schwann cells. Additionally, we observed a significant upregulation of lysosomal exocytosis, characterized by regulated secretion of lysosomal enzymes into the extracellular milieu. Conditioned medium (CM) from CMT1A Schwann cells confirmed elevated CtB and CtD levels and activity. Functional degradation assays confirmed that the CM of CMT1A Schwann cells exhibits increased proteolytic activity, resulting in enhanced degradation of the extracellular matrix (ECM) protein collagen IV compared to healthy controls. Consistent with these findings, reduced ECM protein levels were detected in sciatic nerves of C3 mice compared to WT littermates. Our results underscore lysosomal upregulation, destabilization, and amplified extracellular cathepsin release in CMT1A Schwann cells, contributing to ECM breakdown. Hence, targeting extracellular cathepsin activity may represent a promising therapeutic strategy for CMT1A.