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

Poster P8

Cellular stress responses induced by PMP22 overexpression in Charcot-Marie-Tooth disease type 1A

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Charcot-Marie-Tooth (CMT) disease is the most common peripheral neuropathy, affecting 1 in 2500 people worldwide. The most common subtype, CMT1A, is predominantly demyelinating and is caused by a duplication of the peripheral myelin protein 22 (PMP22) gene, mainly expressed in Schwann cells (SC). However, the mechanisms by which PMP22 overexpression disrupts SC function remain unclear. We hypothesize that PMP22 overexpression induces endoplasmic reticulum (ER) stress through protein overload, which may exacerbate mitochondrial dysfunction, contributing to SC impairment. Given the role of mitochondria-associated membranes (MAMs) in ER-mitochondria communication, we further explored their contribution to ER and mitochondrial stress in CMT1A.

Sciatic nerve tissue and primary SC were isolated from the C3-PMP22 CMT1A mouse model and wild-type controls. Furthermore, we used Schwann cell precursors (SCP) and immature iPSC-derived SC (iPSC-SC), derived from CMT1A patient-induced pluripotent stem cells (iPSCs) and isogenic controls.

Immunocytochemistry indicated increased protein ubiquitination in CMT1A SCP and C3-SC, and increased ER chaperone calnexin intensity in C3-SC. ER stress markers revealed a non-significant increase in BiP/GRP78 in CMT1A SCP, and a non-significant decrease in XBP1s and p-eIF2α/eIF2 ratio in CMT1A SCP compared to controls. Live-cell mitochondrial imaging using MitoTracker Green revealed increased mitochondrial density in C3-SC and CMT1A SCP. Lastly, live-cell confocal imaging using MitoTracker Green and ER-Tracker Red demonstrated reduced ER-mitochondria contact sites in CMT1A SCP, further supported by decreased PE/PC ratios in CMT1A iPSC-SC, suggesting MAM dysfunction.

Our findings indicate activation of the integrated stress response, alongside ER and mitochondrial alterations and reduced mitochondria-ER contacts in CMT1A. Further research is needed to clarify how these changes affect SC myelination and contribute to CMT1A pathogenesis.