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Poster P6

Phenotypic and functional impairments in human CMT1A Dental Pulp Stem Cell-derived Schwann cells

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CMT1A is the most prevalent type of CMT, which is caused by the duplication of the peripheral myelin protein 22 (PMP22) gene, resulting in peripheral nerve demyelination. The failure of many candidate therapies reflects a shortage of physiologically relevant human Schwann cell models. iPSC-derived Schwann cell precursors are valuable, but immaturity and the need for reprogramming raise the need for alternatives.

Dental Pulp Stem Cells (DPSC) reside in adult human teeth and share a neural crest origin with Schwann cells. They can be efficiently differentiated into DPSC-derived Schwann cells (DPSC-SC). Hence, we suggest patient-derived DPSC-SC as a highly translatable in vitro model to research Schwann cell behavior and interactions in CMT1A. DPSC were isolated from third molars of four CMT1A donors and age-matched controls. Following DPSC-SC differentiation, Schwann cell phenotypes were evaluated using RNA sequencing, qPCR, ICC, and proliferation assays. Next, cells were co-cultured with human iPSC-derived motor neurons (iPSC-MN) in 2D microfluidic chambers and 3D collagen type I hydrogels.

RNA sequencing revealed downregulated differentiation, cytoskeletal, and motility pathways in CMT1A, but proliferative and ECM pathways were upregulated. Additionally, MPZ and laminin proteins decreased in CMT1A DPSC-SC, while levels of the immature marker P75NTR increased. CMT1A DPSC-SC showed higher proliferation rates but decreased migration to iPSC-MN in microfluidic co-cultures. Finally, in 3D hydrogels, CMT1A DPSC-SC showed lower contractile function and decreased pericellular density of collagen fibers, compared to controls.

To conclude, our results suggest that CMT1A DPSC-SC display a more immature, repair-like phenotype compared to control cells with disruptions in migration and collagen-linked contraction, which may underlie the pathology. These 2D and 3D patient-specific models provide a reproducible and translatable platform for mechanistic studies and drug screening.