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Studying Organoid Phenotypes of CoQ10-deficient Glomerulopathy

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Objectives : Monogenic causes of steroid resistant nephrotic syndrome (SRNS) account for 11-30% of childhood. Genes involved in coenzyme Q10 (CoQ_{10}) biosynthesis, such as PDSS2, COQ2, COQ6 and ADCK4, are well established causes of SRNS and focal segmental glomerulosclerosis (FSGS). CoQ_{10} is a component of the mitochondrial inner membrane which plays an important role in supporting electron transport of oxidative phosphorylation and protection from oxidative stress. CoQ_{10}-deficient glomerulopathy can be partially treated by CoQ_{10} supplementation, but the therapeutic efficacy of this treatment is variable and has limitations. We here established an in vitro model system of CoQ_{10}-deficient glomerulopathies to study the therapeutic effects of drugs through elaborate manipulations, enabling a better understanding of the disease and the development of more effective treatment.
Methods : We generated CoQ_{10}-deficient kidney organoids from human induced pluripotent stem cells (iPSCs) using the well-established in vitro induction protocol. To establish CoQ_{10}-deficient human iPSCs, we used synthetically generated gRNAs targeting PDSS2 along with Cas9 protein. We performed immunostaining and light microscopy analysis to evaluate the extent of their differentiation. We also observed mitochondrial morphology using electron microscopy to investigate the phenotypic characteristics due to CoQ_{10} deficiency.
Results : Podocytes in kidney organoids display an primary processes and cell-cell junctions, resembling the early stages of foot process formation. No significant differences were observed between the control and PDSS2 knockout kidney organoids, suggesting that PDSS2 ablation does not affect podocyte development. Examination of the ultrastructure of podocytes in CoQ_{10}-deficient kidney organoids revealed that PDSS2 knockout podocytes contained abnormal mitochondria characterized by hyperproliferation and increased size compared to those in control podocytes.
Conclusions : In conclusion, we have developed a modeling system of CoQ_{10}-deficient glomerulopathy using PDSS2 knockout kidney organoids and showed abnormal mitochondrial phenotypes. This system offers a promising platform for evaluating potential drug therapies, thereby contributing to the advancement of treatment options for this condition.