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Using human iPSC derived hepatocyte system models cholestasis with tight junction protein 2 deficiency

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The truncating mutations in tight junction protein 2 (TJP2) cause progressive cholestasis, liver failure, and hepatocyte carcinogenesis. Due to the lack of effective model systems, there are no targeted medications for the liver pathology with TJP2 deficiency. We leveraged the technologies of patient-specific induced pluripotent stem cells (iPSCs) and CRISPR genome-editing, and we aim to establish a disease model which recapitulates phenotypes of patients with TJP2 deficiency. In Transwell and Matrigel sandwich culture systems, the hepatocyte-like cells differentiated from iPSCs with TJP2 mutations exhibited intracellular inclusions of disrupted apical membrane structures, distorted canalicular networks, altered distribution of apical and basolateral markers/transporters. The directional bile acid transport of bile canaliculi was compromised in the mutant hepatocytes, resembling the disease phenotypes observed in the liver of patients. Our iPSC-derived *in vitro* hepatocyte system revealed canalicular membrane disruption in TJP2 deficient hepatocytes and demonstrated the ability to model cholestatic disease with TJP2 deficiency to serve as a platform for further pathophysiologic study and drug discovery.

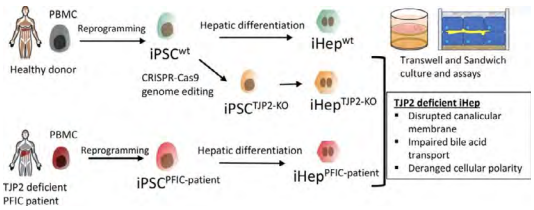

Figure 1: Generation of iPSC derived hepatocytes (iHep) with TJP2 truncating mutations from patient's cells and CRISPR-CAS9 genome-editing technology. Transwell and Matrigel sandwich culture platforms are used for disease phenotype investigation. TJP2 deficient iHeps demonstrated disrupted canalicular membrane, impaired bile acid transport, deranged cellular polarity

Speaker Biography

Chao Zheng Li has his expertise in stem cell related disease modelling and passion in translational medicine. His iHep based functional assays opened opportunities for many genetic/drugs induced cholestasis' mechanistic study and drug screen. He has built this model after years of wet-lab research in stem cell and disease modelling at CGTRM King's College London. His work is based on the well-established 4 stages iHep differentiation protocol (Blackford et al., 2019). This approach largely focuses on generating mature iHeps from iPSC in large quantity via a simple, 2D, chemical based approach. The differentiated iHeps can then integrate into transwell/Matrigel to create high throughput/content disease model for cholestasis research.

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