Human assembloids recapitulate periportal liver tissue in vitro

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Abstract

The development of complex multicellular human in vitro systems holds great promise for modelling disease and advancing drug discovery and tissue engineering. In the liver, despite the identification of key signalling pathways involved in hepatic regeneration, in vitro expansion of human hepatocytes directly from fresh patient tissue has not yet been achieved, limiting the possibility of modelling liver composite structures in vitro. Here we first developed human hepatocyte organoids (h-HepOrgs) from 28 different patients. Patient-derived hepatocyte organoids sustained long-term expansion of hepatocytes in vitro and maintained patient-specific gene expression and bile canaliculus features and function of the in vivo tissue. After transplantation, expanded h-HepOrgs rescued the phenotype of a mouse model of liver disease. By combining h-HepOrgs with portal mesenchyme and our previously published cholangiocyte organoids, we generated patient-specific periportal liver assembloids that retain the histological arrangement, gene expression and cell interactions of periportal liver tissue, with cholangiocytes and mesenchyme embedded in the hepatocyte parenchyma. We leveraged this platform to model aspects of biliary fibrosis. Our human periportal liver assembloid system represents a novel in vitro platform to investigate human liver pathophysiology, accelerate drug development, enable early diagnosis and advance personalized medicine.