Human liver cholangiocyte organoids capture the heterogeneity of in vivo liver ductal epithelium

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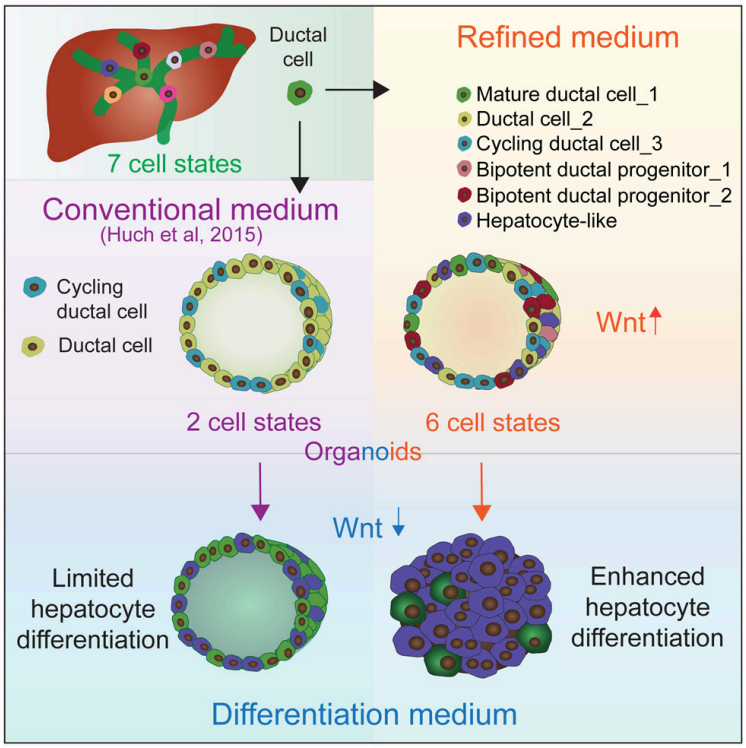
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Abstract

Human liver ductal epithelium is morphologically, functionally, and transcriptionally heterogeneous. Understanding the impact of this heterogeneity has been challenging due to the absence of systems that recapitulate this heterogeneity in vitro. Here, we found that human liver cholangiocyte organoids do not retain the complex cellular heterogeneity of the native ductal epithelium. Inspired by the knowledge of the cellular niche, we refined our previous organoid medium to fully capture the in vivo cellular heterogeneity. We employed this refined system to analyze the relationships between human biliary epithelial cell states. In our refined model, cholangiocytes transition toward hepatocyte-like states through a bipotent state. Additionally, inhibiting WNT signaling enhances the differentiation capacity of the cells toward hepatocyte-like states. By

capturing the in vivo cholangiocyte heterogeneity, our improved organoid model represents a platform to investigate the impact of the different liver ductal cell states in cell plasticity, regeneration, and disease.