Expandable liver organoids generated from human chemically derived hepatic progenitor enable alcoholic liver modeling

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Background: Liver organoids, an attracting source for studying cell to cell interaction, drug screening, and disease modeling in three-dimension systems were demonstrated to be developed from EpCAM⁺ cells. Our group previously reported chemically derived hepatic progenitors (hCdHs), reprogrammed from human primary hepatocytes with bi-potent differentiation capacity and EpCAM⁺ feature. Therefore, we aimed to generate organoids showing characteristics of liver organoids using hCdHs.

Methods: To generate hCdHs, human primary hepatocytes were cultured with reprogramming medium including HGF, A83-01 and CHIR99021 for 7 days. Isolated human liver cells and hCdHs were cultured on Matrigel with organoid medium to generate human adult liver organoids and hCdHs derived liver organoids (hCdHO).

Results: hCdHO were morphologically undistinguished and showed high generation efficiency compared with human adult liver organoids. hCdHO were stably expanded over a 6-month period and expressed liver organoid-specific markers. hCdHO cultured in hepatic differentiation medium showed increased expression of hepatic markers and functional capacity such as CYP activity. Upon transplantation in FRG mice models, hCdHO effectively repopulated the injured liver. We further developed an alcoholic liver model using hCdHO cultured in hepatic differentiation medium under ethanol treatment which presented us with alcoholic liver disease associated alternations in mitochondrial membrane potential.

Conclusions: Our studies suggest that hCdHO have a potential to be a novel liver organoid cell source for performing disease modeling.

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