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Expandable Liver Organoids Generated From Human Chemically Derived Hepatic Progenitor Enable Alcoholic Liver Modeling

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Background : As is currently well known, the organoid model is widely used for the study of disease modeling and drug screening. The generation of liver organoids is due to the presence of EpCAM +, which is expressed mainly in ductal cells. In our research group we develop chemically derived hepatic progenitors (hCdHs) cells, reprogrammed from human primary hepatocytes (hPHs) with EpCAM-positive characteristics, which gives them a better generation capacity for more than 6 months.

Methods : hPHs were cultured with reprogramming medium (HGF, A83-01 and CHIR99021) for 7 days to generate hCdHs. Human liver cells and hCdHs were cultured on Matrigel with organoid medium to generate human adult liver organoids (hALOs) as a control and hCdHs derived liver organoids (hCdHOs) respectively.

Results : hCdHO did not present morphological differences with the hALOs. Hepatic differentiation of organoids (hCdHO_DM) increased the expression of both hepatic and functionality markers, as well as the transcriptional analysis showed that hCdHO_DM were clustered with hPHs after hepatic differentiation. The transplantation of hCdHO into FRG mice increased the survival percentage compared to controls. The alcohol liver damage model in the organoids presented pathophysiological changes similar to those observed in patients.

Conclusions : hCdHOs show a potential to be an excellent organoid cell source to regenerative medicine and disease modeling studies.

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