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Establishment Of Intrahepatic Cholangiocarcinoma Cancer Modelling By CRISPR-Cas9 On Chemically-derived Hepatic Progenitor Organoid

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Background : Intrahepatic cholangiocarcinoma (iCC) is a fatal malignancy of the biliary epithelial cells in the liver. This cancer has a high degree of heterogeneity, is extremely difficult to treat, and has a severely low survival rate. A vital discovery that significantly advances cancer research is the development of disease modelling technology like the cancer organoid technique. These organoids can be generated from iCC patients' tissue specimens but with limited efficiency due to insufficient sample size. In addition, cancer organoids can be derived from normal adult stem cells subjected to CRISPR gene editing to simulate the gene mutation that occurred during early carcinogenesis.

Methods : To generate the iCC cancer organoid model, we co-transfected normal human chemically-derived hepatic progenitor cells (hCdHs) with CRISPR-Cas9 plasmid and gRNA plasmids for TP53 and BAP1. Following the transfection, we generated cancer organoids from these mutant cells and performed various analyses of this cancer disease organoid model.

Results : To overcome the current limitation of the patient-derived cancer organoid, we successfully generated cancer organoids from hCdHs that can be robustly expanded from a relatively small cell number. Then, we introduced the double knock-out of TP53 and BAP1, a well-established iCC cancer driver gene. These CRISPR-engineered hCdHs-derived cancer organoids showed comparable phenotypes with the original iCC tumour malignant features.

Conclusions : These results demonstrated the capability of our CRISPR-engineered hCdHs-derived cancer organoid as a powerful cancer disease modelling platform.

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