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Production of chemically derived hepatic progenitor from human hepatocytes using small molecules

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Introduction : Cell-based regenerative medicine is a breakthrough technology, which holds promises for gene and/or stem cell therapy and given the shortage of donor organs, may provide a valuable option for patients with end stage of liver disease. Despite much progress in isolation and long-term expansion of bipotent progenitor cells with regenerative capacity from terminally differentiated mouse hepatocytes, expansion of the adult human hepatocytes remains a major challenge.

Methods : We report a successful generation of the patient-specific hepatic progenitor cells from human hepatocytes from healthy and disease liver using two small molecules and growth factor.

Results : After three days of treatment small molecule in the presence of growth factor, a key driver of hepatic progenitor cell activity, triggered expansion of small polygonal cells, which co-expressed known hepatic progenitor cells and lineage specific marker genes. These chemically derived human hepatic progenitor cells (hCdHs) could self-renew for at least 10 passages while retaining phenotype, normal karyotype and potential to differentiate into functional hepatocytes and biliary epithelial cells in vitro. A next-generation sequencing confirmed a high degree of molecular similarity between hCdHs and human hepatoblasts. Upon intrasplenic transplantation into immunocompromised mice with a diseased liver, hCdHs effectively repopulated and restored.

Conclusions : In conclusion, hCdHs provide a safe novel tool that permits expansion and genetic manipulation of patient-specific hepatic progenitor cells to study regeneration and repair of diseased liver.

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