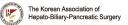
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Epigenetic Modulation Inhibits Epithelial-mesenchymal Transition-driven Fibrogenesis And Enhances Hepatic Progenitor Characteristics Of Chemically-derived Hepatic Progenitor Cells

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Background : One of the novel cell sources of cell-based liver regenerative medicine is human chemicallyderived hepatic progenitor cell (hCdHs), which is generated by direct hepatocyte reprogramming with a combination of small molecules (HGF, A83-01, CHIR99021). However, there have been several issues concerning the cell's stability and maintenance, namely the occurrences of epithelial-mesenchymal transition (EMT) that develop fibrotic phenotype, resulting in the loss of hepatic progenitor characteristics. These hepatic progenitor attributes are thought to be regulated by SOX9, a transcription factor essential for hepatic progenitor cells and cholangiocytes.

Methods : To suppress the fibrotic phenotype and improve our long-term hCdHs culture technology, we utilized the epigenetic drugs DNA methyl transferase inhibitor (DNMTi, 5-azacytidine) and histone deacetylase inhibitor (HDACi, sodium butyrate) that have been reported to suppress and revert hepatic fibrosis. To confirm the essential role of SOX9 to our cell, we uses CRISPR interference (CRISPRi) to repress the SOX9 expression.

Results : The treatment of only 5-azacytidine significantly reduces the fibrosis/mesenchymal marker and EMT-related transcription factor expression level in the early passages. Interestingly, this treatment also increased the hepatic progenitor markers expression, even during the reprogramming phase. Then, we confirmed the essential role of SOX9 by repressing the SOX9 expression with CRISPRi that resulted in the down-regulation of several essential hepatic progenitor cell markers.

Conclusions : These results demonstrated the tremendous effect of DNMTi 5-Azacytidine to inhibit EMTdriven hepatic fibrosis and the significance of SOX9 to the hepatic progenitor cell stemness properties.

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