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**Generation of Induced Hepatocyte-Like Cells From Bone Marrow Mesenchymal Stem Cells Derived From an α1, 3-Galactosyltransferase Knockout Pig**

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Transplantation of porcine hepatocytes for the treatment of humans with acute and chronic liver diseases is considered an alternative to liver transplantation treatment. Especially, a bioartificial liver using porcine hepatocytes has the potential to facilitate liver transplantation for patients with acute-on-chronic liver failure. However, the use of porcine primary hepatocytes is limited by their low survivability under in vitro culture systems and complicated methods of isolation. To address this concern, we attempted to generate induced hepatocyte-like cells from bone marrow mesenchymal stem cells (BM-MSCs) derived from an α1, 3-Galactosyltransferase knockout (GalT KO) pig by transfecting three hepatocyte transcription factors (HNF1A, HNF4A, and FOXA3) and an additional small molecule such as A83-01, an inhibitor of TGF-ß receptor. BM-MSCs derived from the GalT KO pig could be used to minimize immune rejection in xenotransplantation in the future. The ratio of BM-MSCs and the three lentiviral vectors was maintained at MOI =1 and at one day post infection, they were cultured in a hepatocyte culture medium with or without 2 μM A83-01 for 4 weeks. Porcine induced hepatocyte-like cells (pHeps) were observed at a low frequency from 1 week onwards, regardless of A83-01; however, the presence of A83-01 increased the colony number of pHeps. Up to 4 weeks, pHeps maintained A83-01 treatment group but not without A83-01. qPCR analysis of liver-specific genes such as albumin and transferrin genes revealed that A83-01 improved the expression of these genes in the pHeps. Notably, A83-01 treatment could induce the activation of endogenic genes (pHNF1A, pHNF4A, and pFOXA3) in pHeps, as indicated by qPCR results. These results suggest that pHeps could be generated using the three mentioned factors, although at a low efficiency, and that A83-01 could improve the efficiency of pHep generation by the inhibition of epithelial-to-mesenchymal transition. These findings provide valuable information in the field of translational liver research and testing cells for the development of a bioartificial liver system and novel pharmaceuticals.

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**Technique for Orthotopic Liver Transplantation in Cynomolgus Monkeys (Macaca Fascicularis)**

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**Purpose:** Recent studies investigating new strategies to modulate the immune system have utilized animal models of liver transplantation (LT)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\). However, the anhepatic phase (AHP) remains a crucial problem in experimental LT\(^6\)\(^7\). The aim of the present study is to introduce a technique for successful orthotopic liver transplantation in cynomolgus monkeys using an early-reperfusion strategy.

**Methods:** Orthotopic allo-LT was performed with seven donor/recipient pairs of cynomolgus monkeys. In two recipients, liver allografts were perfused after supra-hepatic inferior vena cava (SHIVC), portal vein (PV), and infra-hepatic inferior vena cava (IHIVC) anastomosis. To reduce the time of AHP in five recipients, liver allografts were perfused after SHIVC and PV anastomosis while the IHIVC was not anastomosed.

**Results:** In the latter strategy, the AHP was reduced from 46 minutes to 31 minutes and a 24-hr survival rate of 80% was achieved.

**Conclusion:** Our results indicate that an early-reperfusion strategy can be successfully used to establish a LT model in cynomolgus monkeys with a consistently high rate of animal survival.

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