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Transplantation Of Personalized 3D Artificial Bile Duct With Chemically Reprogrammed Hepatic Progenitors

Myounghoi KIM[1], Suk-Hee PARK[2], Jaemin JEONG[1], Han Joon KIM[1], Dongho CHOI*[1]

[1]*Department Of Surgery, Hanyang University College Of Medicine, Seoul, REPUBLIC OF KOREA*
[2]*School Of Mechanical Engineering, Pusan National University, Busan, REPUBLIC OF KOREA*

Background : Cholangiopathy is a variety spectrum including chronic progressive bile duct disorders with limited treatment options. 3D bioengineering with stem cell-based is emerging as a new therapy tool for construction of functional tissues and hold great promise for regeneration medicine.

Methods : To demonstrate safety and adequacy for the in vivo transplantation, we manufactured 3D artificial bile duct (ABD) based on the MRI data of rabbit common bile duct (CBD). We manufactured tubular scaffold with nano- and micro- mixed fibrous using electrospinning to enhance hCdHs attachment of the inner electrospun fibrous layer as well as mechanical stability of outer layer. We previously reported that reprogrammed primary hepatocytes (hPHs) to human chemically derived hepatic progenitors "hCdHs" by using three small molecules (A-83-01, CHIR99021 and hepatic growth factor (HGF)). We seeded hCdHs inside of ABD and differentiated it to cholangiocyte (hCdH-Chols) undergo cholangiocyte differentiation medium (CDM) condition for 14 days. Finally, we transplantation the ABD with hCdH-Chols to middle in common bile duct of rabbit and monitored.

Results : First, we confirmed that hCdHs and hCdH-Chols showed each state markers expression and differentiation capacity hCdHs to hCdH-Chols by performing RT-qPCR and immunostaining. The hCdH-Chols showed cholangiocyte gene expression profiles and function in 2D and 3D. When cultured the hCdHs inside of ABD for 14 days with CDM, the hCdHs successfully differentiated to hCdH-Chols, showed line formation followed as inner layer that is one of biliary epithelium feature as well as cholangiocyte markers expression. Finally, we performed that resected mid portion of common bile duct (CBD) of rabbits and inserted the ABD with hCdH-Chols to demonstrate the stability and functionality of in vivo experiment. The complete blood count (CBC) and biochemistry results in blood displayed that the liver damage markers (AST, ALT and ALP) reduced as time goes on, while ductal damage marker (TBIL) was in reference range for 42 days. Notably, the rabbits that transplanted the ABD-hCdH-Chols was given survival capacity longer than control rabbits (empty ABD).

Conclusions : Our system could promise that provide a scalable and compatible platform for cholangiopathy, and it may contribute to manufacture patient-specific bile duct for clinical application.

Corresponding Author : **Dongho CHOI** (crane87@hanyang.ac.kr)