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研究課題名	Reconstruction of human liver in Fah-/-Rag2-/-IL2rg-/- rats with hiPSC derived liver organoids	
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(Form 2-2)

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Report

In this year, we tried to characterize proliferative hepatoblast from hiPSCs and evaluate their repopulation capacity in $Fah^{-/-}Rag2^{-/-}IL2rg^{-/-}$ (FRG) rats. First, we performed RNA sequence analyses to characterize the hepatoblast after repeated passages. Compared with hiPSC and primary human hepatocytes, the passaged cells maintained high expression of hepatoblast-specific signatures. Principal component analysis and correlation analysis demonstrated that the different passaged hepatoblast had a similar whole transcriptomic signature. Flow cytometry and immunostaining analyses also showed that the passaged hepatoblast maintained the expression of hepatoblast markers. Moreover, these passaged cells could be differentiated into hepatocytes and cholangiocytes. Next, we optimized the NTBC cycle to induce liver injury in FRG rats. Using the published NTBC cycle protocol, we noticed an extremely weak injury in FRG rats, making it difficult for hepatoblast to colonize in the liver. When reducing the dose of NTBC, the serum injury markers were increased. We then transplanted hepatoblast in this optimized injury model and successfully detected human Albumin production in rat serum after four weeks of transplantation, while a decline production of human Albumin was detected at eight weeks of transplantation. These results indicate that the generated proliferative hepatoblast could engraft in FRG rats, but how to promote the repopulation capacity should be further investigated.