Shota Sasaki et al., J Biomed Eng Med Devic 2017, 2:2 (Suppl)
DOI: 10.4172/2475-7586-C1-003

Application of hepatocyte nuclear factor 4γ for establishment of differentiated hepatocytes

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Hepatocytes play a central role in drug metabolism in liver. In pharmacokinetics tests of new drugs, normal human hepatocytes have been used for evaluation of the drugs. However, supply of the hepatocytes is unstable and it costs expensive. Thus, development of efficient hepatocyte differentiation system using ES and iPS cells has been desired for a long time. Previous studies showed that hepatocyte nuclear factor 4α (HNF4α), an orphan member of the nuclear receptor superfamily and a master regulator in liver homeostasis, is an essential factor for differentiation of hepatocytes from hepatoblasts and iPS cells. In addition to HNF4α, HNF4 family contains other isoform, HNF4γ in mammals. Because hepatic HNF4γ is hardly detected in normal liver, function of HNF4γ remain to be clarified. We found that hepatic expression of HNF4γ is markedly up-regulated in liver-specific Hnf4α-null mice. Furthermore, two HNF4γ variants that have different N-terminal exon, known HNF4γ1 and novel HNF4γ2, are also up-regulated in the Hnf4α-null mice. Therefore, we investigated whether the HNF4γ variants induce transcriptional activity and mRNA expression of the HNF4α target genes. As a result, HNF4γ2, but not HNF4γ1 was found to have strong transcriptional activity and induce expression of many liver-enriched genes in HCC-derived HepG2 cells when compared to HNF4α, suggesting that HNF4γ2 could be a new hepatocyte redifferentiation factor. These findings may contribute to establishment of differentiated hepatocytes using ES and iPS cells and development of HCC therapy by introducing HNF4γ2.

Recent Publications

1.A Moriimoto, Sasaki S, et al. (2017) An HNF4α-microRNA-194/192 Signaling Axis Maintains Hepatic Cell Function. J Biol Chem; 292(25): 10574-10585.

2.S Matsuo, Shota Sasaki, et al. (2016) Hepatocyte Nuclear Factor 4α Controls Iron Metabolism and Regulates Transferrin Receptor 2 in Mouse Liver. J Biol Chem.; 290(52): 30855-65.

Biography

Shota Sasaki is currently pursuing Science and Technology Doctoral course in Gunma University. He has published 2 papers in reputed journals.

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