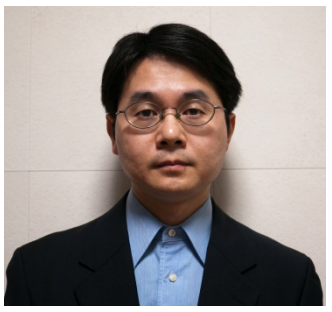
東海大学創造科学技術研究機構
TOKAI UNIVERSITY INSTITUTE OF INNOVATIVE SCIENCE AND TECHNOLOGY

Laboratory of Stem Cell Therapy KAMIYA LAB
紙谷研究室



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Establishment of Cell Therapies for severe liver diseases using hepatic stem/progenitor cells

Keywords: Hepatic stem cell, iPS cell, Liver regeneration, Liver development

Background and Motivation

Liver is the central organ of metabolism and hepatocytes, the main cellular component of the adult liver, express many enzymes and factors playing a crucial role in mature liver functions. Infection of hepatitis viruses, overtake of alcohol, or several metabolic disorders induce chronic liver hepatitis, liver fibrosis, and hepatocellular carcinomas. In this laboratory, we are going to establish new stem cell therapy for these severe liver diseases.

Using our purification methods and *in vitro* culture systems of hepatic stem/progenitor cells (HSPCs), we have several research plans.

1. Analyses of molecular mechanisms of proliferation and differentiation of HSPCs.

HSPCs have high proliferative ability and bi-potency for differentiation into both mature hepatocytes and cholangiocytes. However, HSPCs could not be expanded with sustained bi-potency over a long period of time, suggesting that the present culture system is insufficient to maintain self-renewal activity. We are going to search genes regulating stemness of HSPCs for establishment of the efficient culture system.

2. Differentiation of human pluripotent stem cells into HSPCs for stem cell therapy .

Embryonic stem (ES) cells and induced pluripotent stem (iPS) cells contain multipotency to differentiate into specialized cells of the three primary germ layers and can grow for a long time in vitro. These cells are very useful to regenerative medicine for several diseases. I have research plans to analyze molecular mechanisms regulating proliferation and differentiation of HSPCs derived from human iPS cells.

Originality

Human hepatocytes are expensive and variable because these cells are derived human donor livers. Several research groups have developed the culture methods which induce differentiation of human ES and iPS cells directly into mature hepatocytes. However, *in vitro* expansion of mature hepatocytes is very difficult. In my research plan, a lot of functional hepatocytes will be made using two step methods; (1) HSPCs, which contain high proliferative activity, are purified from fetal and adult livers or induced from human iPS cells. (2) After long-term culture for expansion, HSPCs are induced to differentiate into functional hepatocytes *in vitro*.

Impact and Perspective

Liver is the central organ for detoxification of drugs. During drug development for diseases, many candidate compounds are stopped in pre-clinical research because of their liver toxicity. Cultured hepatocytes with high-level of metabolic functions are required for cell therapy for liver diseases, analyses of metabolism and toxicity during drug development, and artificial livers for the treatment of acute liver failure. For these purposes, we will establish new culture methods for proliferation and differentiation of hepatic stem/progenitor cells.

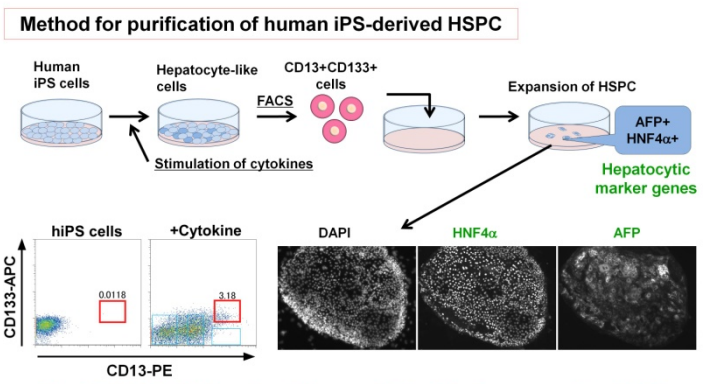

Fig 1. Differentiation of human pluripotent stem cells into HSPCs

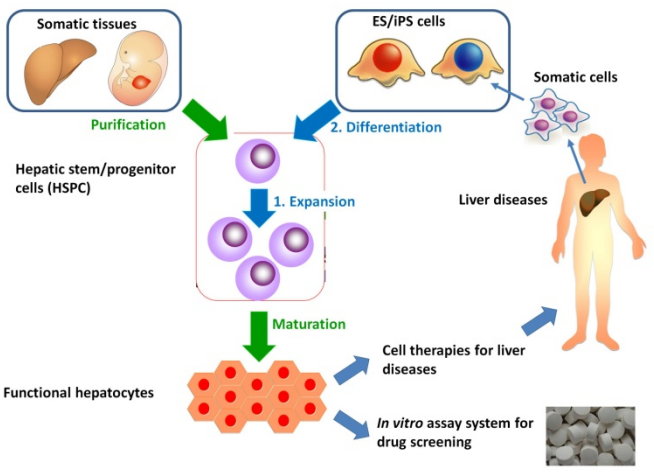

Fig 2. The strategy of stem cell therapies for liver diseases

■ For more information:

www.u-tokai.ac.jp/tuiist/english/tt/announcement_kamiya.html

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