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Patient specific stem cell technology for disease modeling and drug testing

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Human induced pluripotent stem cells (iPSCs) are potential sources of hepatocytes for liver transplantation, drug screening and toxicity testing. In vitro differentiation of human iPSCs into hepatic cells has been achieved using multistage differentiation protocols. However it has not been clear whether these cells are truly functional (i.e. are they capable of regenerating diseased liver tissue, and functional enough to model liver diseases and to test new drugs?). To answer these questions, we have extensively studied both in vivo and in vitro properties of human iPSC derived hepatic cells.

Based upon our in vivo study, human iPSC-derived hepatic cells at various differentiation stages can engraft liver in a mouse liver cirrhosis model. We also assessed the ability of various origin human iPSC lines (derived from each of the three developmental germ layer tissues) to regenerate mouse liver. These iPSC lines, with similar but distinguishable global DNA methylation patterns, differentiated into multistage hepatic cells with an efficiency similar to that of embryonic stem cells. Human hepatic cells at different differentiation stages derived from the various origin iPSC lines successfully repopulated the liver tissue of mice with cirrhosis, and secreted human-specific liver proteins into mouse blood with comparable levels to human primary hepatocytes. These results demonstrate the liver regenerative capabilities of human iPSC-derived hepatic cells in vivo and suggest that efficient hepatic differentiation and regeneration can be achieved from iPSCs of distinct origins regardless of their parental epigenetic memory.

In order to model both inherited and acquired liver diseases, we have developed two new technologies for reprogramming of 1) Epstein-Barr virus (EBV) immortalized B lymphocyte cell lines and 2) primary human hepatocytes into iPSCs. Since EBV-B-lymphocyte cell lines have been widely banked for studying a variety of diseases, these cell lines represent an important resource for iPSC based disease modeling. For modeling acquired liver diseases using iPSCs it is essential to establish a technology for reprogramming primary hepatocytes which would contain disease associated somatic mutations. We have generated disease-specific iPSCs from both of these cell types. Using some of these disease specific iPSC lines and our hepatic differentiation protocol, we have successfully modeled a metabolic liver disease in a dish and have recently discovered multiple potential drugs using the cellular model. These results also support the in vitro functionality of the iPSC-derived hepatocytes. These studies will provide a foundation to generate other liver disease models to discover/develop novel drug therapies for many incurable liver diseases including liver cirrhosis and liver cancers

Biography

Yoon-Young Jang has completed her M.D. and Ph.D from S. Korea and postdoctoral studies from Johns Hopkins University School of Medicine. She is the director of Stem cell biology laboratory at Hopkins SKCCC. She has published more than 45 papers in reputed journals including Nature Cell biol and Science Transl Med, and serving as an editorial board member of multiple scientific journals

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