Institutionen för klinisk vetenskap, intervention och teknik, Enheten för Transplantationskirurgi, Karolinska Institutet

Cellular Replacement Therapy for Liver Disease

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Abstract

Liver disease is a major health problem worldwide. The liver performs a wide range of functions, which the human body cannot survive without. The human liver is continuously challenged with infectious organisms, alcohol and chemicals, congenital defects, autoimmunity and malignancy etc. The liver has been imparted a marvelous capacity to regenerate and recover from various insults. However, in many cases liver injuries exceed its regenerative capacity with end-stage liver disease becoming the inevitable end.

So far, liver transplantation is still the only treatment modality for end-stage liver disease. However, there are many limitations to liver transplantation towards its applicability and availability for all patients worldwide, such as scarcity of donors as well as other ethical, technical and surgical considerations.

Cell transplantation is a frequently studied alternative to organ transplantation in liver disease. Many cell types are under extensive evaluation, with primary human hepatocytes and different stem cell types coming first on the list. For primary human hepatocytes, liver tissue is still needed, and when available, cells are produced in huge numbers requiring cryopreservation. Available hepatocyte cryopreservation protocols still need further optimization. In addition, better cold storage techniques for hepatocytes are needed for the feasibility of frequent cell infusions per patient. Stem cells still need to be studied further for their differentiation potential towards hepatic lineages, safety, immunomodulatory roles, and their possible support for co-transplanted hepatocytes.

In this thesis, I addressed a few of the current obstacles facing cellular replacement therapy for liver disease. In the first study, I isolated and characterized a mesenchymal stem cell population from human fetal liver. The hepatic origin, the mesenchymal nature, and the immunomodulatory effects of these cells suggest them as potential candidates for cellular therapy for liver disease. In addition, we transplanted these cells into a mouse model of liver disease with an evidence for their potential differentiation to hepatocyte-like cells \textit{in vivo}. In the second study, we characterized microRNAs expressed in the human liver. Such information can help understanding the role of microRNAs in liver development and their potential use in microRNA-based stem cell differentiation towards hepatic lineages. In the third study, we introduced a new defined xeno-free cryoprotectant to the field of hepatocyte cryopreservation. This cryoprotectant could be of value when preserving hepatocytes and stem cell-derived hepatocytes in a clinical setting. In the fourth study, we showed that human liver material could be better cold-stored as a whole tissue rather than as single cells. This makes it possible for frequent hepatocyte infusions commonly needed in a clinical context.