GÖTEBORGS UNIVERSITET

Experimental models with specific approaches to augment human fetal liver cell engraftment

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Conferencecentrum Wallenberg, Lyktan Hall, Medicinaregatan 20A.
fredagen den 28 march 2014, kl 9.00

av

Pradeep Bhatu Patil
M.V.Sc. (Veterinary Surgery & Radiology)

Fakultetsopponent:
Prof. John Fung
Digestive Disease Institute, Cleveland, Ohio, USA

This thesis is based on the following papers:

I. Fetal liver-derived mesenchymal stromal cells augment engraftment of transplanted hepatocytes.

Meghnad Joshi, Pradeep B. Patil, Zhong He, Jan Holgersson, Michael Olausson, Suchitra Sumitran-Holgersson. *Cytotherapy*, 2012; 14(6): 657-669. (*Published*)

II. Phenotypic and *in vivo* functional characterization of immortalized human fetal liver cells.

Pradeep B. Patil*, Setara Begum*, Meghnad Joshi, Marika I Kleman, Michael Olausson and Suchitra Sumitran-Holgersson. *Scandinavian Journal of Gastroenterology,* 2013 (*In press-Manuscript ID – SGAS-2013-0286.R1*).

III. Chemokine mediated robust augmentation of liver engraftment - A novel approach.

Meghnad Joshi, Mihai Oltean, Pradeep B. Patil, David Hallberg, Marika I Kleman, Jan Holgersson, Michael Olausson and Suchitra Sumitran-Holgersson. *(Manuscript submitted)*

IV. CD271 identifies functional human hepatic stellate cells, which localize in perisinusoidal and portal areas in livers after partial hepatectomy

Pradeep B. Patil*, Meghnad Joshi*, Liza Johannesson, Michael Olausson and Suchitra Sumitran-Holgersson. *(Manuscript submitted)*

* Authors contributed equally to this paper

Supervisor:
Prof. Michael Olausson
Department of Surgery,
Laboratory for transplantation and regenerative medicine, Gothenburg University

Assistant supervisor: Prof. William Bennet
Department of Surgery,
Gothenburg University

Abstract

Experimental models with specific approaches to augment human fetal liver cell engraftment

Pradeep Patil
Department of Surgery, Institute of Clinical Sciences,
Sahlgrenska Academy at University of Gothenburg

Background: Liver disease is a common cause of morbidity and mortality worldwide. Orthotopic liver transplantation has so far been the only available therapy for patients with end-stage liver failure. Unfortunately, the availability of donor organs is limited and more than 40% of patients become too sick to survive each year while waiting for liver transplants. Cellular therapy with stem cells and their progeny is a promising new approach to this largely unmet medical need, but is yet to be integrated into the current clinical system. Impediments in cell transplantation are well characterized, but there is lack of reliable solutions, which has limited the use of this technique to act as a bridge (temporary support) to transplantation.

Aims: Studies covered under the current thesis are focused on validation and evaluation of reliable cell sources and feasible protocols for enhancing their engraftment and proliferation in animal models.

Materials and methods: The mammalian fetal liver contains colony-forming cells with high proliferative potential. The use of human fetal liver cells (hFLCs) is a suitable candidate for the purpose of cell therapy and diagnostics. We have evaluated hFLCs lines as a potential source of stem cells and tested their *in vivo* functions in a model of liver injury using nude mouse.

Results and discussion: This thesis has shown that the regimens of preconditioning (using chemokines) or the co-transplantation (liver cells with mesenchymal stem cells) have the possibility to augment engraftment. Also, manipulating liver cells *ex vivo* to increase longevity helps in growing cell colonies much faster for many passages to produce a limitless population. It also demonstrates a novel marker to isolate adult or fetal liver stellate cells, which has an important role in immunoregulation and liver fibrosis.

Summary: This thesis describes and highlights novel and feasible approaches in liver cell transplantation, with the possibility to improve current clinical protocols.

Keywords: cell transplantation, chemokines, SV40, stellate cell, MSCs

ISBN -– 978-91-628-8933-3
Gothenburg, 2014, vetdrpradip@yahoo.com