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Cell replacement therapy for diabetics by liver to pancreas transdifferentiation

Abstract

Background: Transdifferentiation is the direct reprogramming of adult cells into alternate cell types with different function. Liver to pancreas transdifferentiation (TD) induced by ectopic expression of pancreatic transcription factors (pTFs) was first described by our group both in vivo (1) and in human liver cells in vitro (2).

Aim: Disclose the mechanism that mediate the developmental reprogramming process of adult human liver cells into endocrine pancreatic cells. Determine the developmental barriers that restrict this process efficiency and suggest modalities to increase the process efficiency. Finally, the clinical and industrial translation of adult cells reprogramming will be discussed.

Methods and Results: We have generated primary cultures of liver derived from >100 human donors. The cultures were analyzed for their transdifferentiation efficiency upon transient ectopic expression of pancreatic transcription factors (pTFs). Our data suggest that TD occurs in predisposed liver cells that display specific epigenetic and intracellular characteristics. Moreover, TD-propensity can be extended to most of the cells by epigenetic manipulations, hence, increasing the transdifferentiation efficiency. Moreover, a special role of the vascular niche on the transdifferentiated cells maturation has been characterized. Finally, the human derived insulin producing cells are functional upon in vivo implantation in rodents.

Conclusions: The generation of an autologous insulin producing tissue, by liver transdifferentiation, is expected to alleviate the need for pancreas transplantation or islet cells implantation from cadavers, for treating diabetic patients. This cell replacement therapy approach is expected to overcome the shortage in cadavers' tissues and the following need for anti-rejection treatment. Adult cells are expected to be safer than other potential sources such as embryonic stem cells (ESC) or induced pluripotent cells (IPS), that should be further encapsulated prior to in vivo transplantation. The present cell replacement therapy allows the diabetic patient to be also the donor of his own therapeutic tissue.

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Biography

Sarah Ferber graduated at the Technion under the supervision of Prof. Hershko and Prof. Ciechanover on revealing the biology of the Ubiquitin system for protein degradation (Nobel Prize in 2004). She completed her post-Doctoral studies at Harvard Medical School and moved to Diabetes Cell Therapy in UTSW-Dallas TX.

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