Title: The role of immune and endothelial cells in shaping a regenerative pancreatic islet microenvironment: 3D perspectives.

Description:

Diabetes is a pandemic disorder characterized by hyperglycemia. Current diabetes treatments strive for glycemic control but fail to solve the underlying beta cell defect. Since diabetes patients show a decreased functional beta cell mass, curative strategies should aim at restoring and protecting this mass to reinstate fine-tuned glucose homeostasis. Such cell replacement therapies could rely on transplantation of exogenous beta cells, or on endogenous regeneration of beta cells. Transplantation of exogenous beta cells, either from cadaveric donor islets or derived from stem cells, is a valid therapeutic strategy. However, the transplantation sites are functionally different in terms of neurovascular integration from the pancreas, which is the most appropriate environment for physiological integration of islet grafts. Beta cell regeneration from cells within the pancreas is a particularly attractive strategy as it offers additional advantages compared to transplantation by restoring the injured islet microenvironment and thus reinstating true physiological glucose control. Different in vivo approaches of beta cell regeneration are currently explored: (i) reactivation of adult pancreatic endocrine progenitors, (ii) replication of remaining beta cells, and (iii) reprogramming of other pancreatic cell types to beta cells [3]. These strategies rely on reactivation of the proendocrine master transcription factor neurogenin 3 (NEUROG3) and the interaction with nonendocrine islet cell types including immune and endothelial cells. However, the mechanistic details of adult beta cell regeneration are poorly understood, and the intercellular crosstalk has been understudied due to challenges in 3D imaging of pancreas. We will use innovative clearing protocols optimized for pancreas and light sheet fluorescent microscopy to unveil the contribution of immune cells and vascular endothelial cells in several in vivo models of beta cell regeneration. A better understanding of the 3D islet microenvironment during regeneration could provide key insights to develop a regenerative therapeutic strategy for diabetes.

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