ID: MSCA-19-Heimberg02

Discipline: Medicine and Pharmacy

Title: Designing a microenvironment for beta cell proliferation

Abstract: Beta cells produce insulin, a hormone that controls our energy homeostasis. Diabetes is caused by an insufficient number of beta cells or when beta cells functionally don't suffice. Beta cell intensively communicate with each other and with other cells in their microenvironment. We hypothesize that dissection of this microenvironment will allow us to generate beta cells in a dish as well as in patients as signals from the microenvironment are essential for the formation of functional beta cells during embryogenesis and postnatally.

Both macrophages and endothelial cells significantly contribute to the beta cell microenvironment. We aim to understand the signals these cell types provide to the beta cells.

Therefore, we characterized a subpopulation of “regenerative” macrophages that is necessary for the formation of beta cells in experimental mice under conditions of tissue damage and regeneration. Following isolation, these macrophages from an injured pancreas appeared to induce beta cell proliferation when transplanted in healthy mice. The macrophages precisely control their activities and won’t provoke unrestrained expansion of the beta cell mass, making them good candidates for clinical intervention.

To investigate the interaction between endothelial cells and beta cells we used transgenic mice that allow conditional interruption of signal transduction by Vascular Endothelial Growth Factor (VEGF). Vessel ablation near beta cells is less dominant than generally accepted. Most remarkable was the increased beta cell mass by proliferation when we allowed endothelial cells to reappear. By adapting the microenvironment under influence of endothelial cells, the beta cell mass can thus be augmented, a major goal in diabetes therapy. The current challenge is to disclose the mechanism behind this phenomenon and translate it to a safe approach for therapy. We provided proof-of-concept by selection of the most logical candidate as (one of the) responsible factor(s), VEGF, and introduced its code (mRNAVEGF) in human beta cells. When transplanted, the mRNAVEGF-treated grafts showed better vascularization and more beta cells compared to control-treated grafts. The feasibility to apply this strategy in patients is high.

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