

Pro-Inflammatory Macrophages Induce Pyroptotic Death of β -Cells: Modeling Macrophage-Mediated Pancreatic Endocrine β -Cell Damage Using Human Pluripotent Stem Cell-Derived Vascularized Macrophage-Islet Organoids

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Diabetes is a leading cause of death and disability worldwide. Loss of functional pancreatic β -cell mass is key to both type 1 (T1D) and type 2 (T2D) diabetes. Islet macrophages have important roles in the pancreas during development and tissue homeostasis. Studies indicate that these macrophages also contribute to β -cell death in T1D and TD2. However, the absence of a model that mirrors the cellular components of the human pancreas makes it difficult to dissect the key pathways involved in islet macrophage-mediated β -cell death. Organoids mirroring human organs can now be generated from human pluripotent stem cells (hPSC). To study the mechanisms by which macrophages induce β -cell death and the crosstalk involved between these cells, I constructed a novel human hPSC-derived vascularized macrophage-islet organoid model consisting of pancreatic endocrine cells, endothelial cells, and macrophages. To find potential mechanisms, I performed a comparative analysis of the organoids in the presence of unstimulated macrophages or pro-inflammatory macrophages. I found phenotypic evidence of pro-inflammatory macrophage-induced pyroptotic death of β -cells, an inflammation-mediated form of programmed cell death. RNA seq analysis showed specific upregulation of genes associated with pyroptosis, including Gasdermin D, Caspase 1, Interleukin-18, High mobility group box 1 (HMGB1), and N-terminal PYRIN-PAAD-DAPIN domain and a C-terminal caspase-recruitment domain (PYCARD). Together these data show that inflammatory macrophage-induced pyroptosis may lead to the loss of β -cell mass in diabetic pancreas. These hPSCs-derived vascularized macrophage-islet organoids provide means for a more systematic understanding of immune cell-mediated damage of host β -cell in diabetes.

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