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Preview

Integrating blood vessel organoids makes stem cell-derived islets more competent

Daniel M. Tremmel,[1,2] Yonglin Zhu,[1,2] and Juan M. Melero-Martin[1,2,3,*]
[1]Department of Cardiac Surgery, Boston Children's Hospital, Boston, MA 02115, USA
[2]Department of Surgery, Harvard Medical School, Boston, MA 02115, USA
[3]Harvard Stem Cell Institute, Cambridge, MA 02138, USA
*Correspondence: juan.meleromartin@childrens.harvard.edu
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Wang et al. present an all-stem-cell strategy that vascularizes pancreatic islet organoids by integrating them with blood vessel organoids, enhancing β cell maturation and resilience and reversing diabetes in mice.[1] The resulting model offers a platform to study islet-vascular biology *in vitro* and to advance transplantation therapies.

Type 1 diabetes (T1D) is caused by autoimmune destruction of β cells, requiring lifelong management of blood glucose through exogenous insulin treatment.[2] β cell replacement therapy through cadaveric pancreas or islet transplantation restores insulin-producing cells to the body and reduces the burden of glucose management on the patient but is limited by organ availability and requires immunosuppression. Recent advances in the generation and transplantation of stem cell-derived islets (sc-islets)[3] have shown that these cells can function and reverse diabetes in animal models and in early clinical trials.[4] However, a major challenge of applying sc-islet cell replacement therapies for T1D is substantial cell death after transplantation, partially due to poor vascularization of the graft.

Blood vessels are more than passive conduits; they are comprised of endothelial cells (ECs) and perivascular mural cells that interact intricately with surrounding tissues to form specialized niches within functional organs. ECs within the islets form fenestrated blood vessels with an organ-specific gene-expression signature and exchange signals with islet endocrine cells. Prior efforts to vascularize islets have used co-cultured endothelial cells (e.g., human umbilical vein endothelial cells [HUVECs]), microvessels, or pre-vascularized transplant sites. These approaches can improve early graft survival, but each has a defining shortfall: the endothelium is not organ matched and lacks the fenestrated, islet-specific capillary phenotype, the donor vessels are frequently regressed or replaced by host vasculature rather than durably integrated, and pre-vascularized sites generate vessels around the graft, leaving intra-islet diffusion distances and the hypoxic core unresolved.[5] The real challenge has been to integrate the two compartments—islet and vascular cells—into a single organotypic unit that can model islet-vascular interactions *in vitro* and enhance revascularization after transplantation to improve survival and augment sc-islet function.

In this study, Wang et al.[1] successfully established an all-stem-cell organoid system, combining sc-islets with blood vessel organoids (BVOs), a self-organizing vascular model of ECs and pericytes that the same group had previously developed.[6] To create vascularized pancreatic islet organoids (VPIOs), the authors encapsulated the BVOs with a dissociated single-cell suspension of sc-islets in AggreWell plates, allowing the islet cells to integrate with vascular structures over 3 days. More extensive sprouting and angiogenesis were achieved when VPIOs were embedded in a collagen/Matrigel matrix, resulting in an intra-islet lumenized vascular network (Figure 1). The co-culture of islet cells with BVOs provides a scalable method to generate uniformly vascularized islets.

Beyond generating vessels, co-culture promoted organotypic endothelial specification and β cell maturation. The ECs adopted a fenestrated morphology, reminiscent of native islet vasculature, and became transcriptionally similar to pancreatic ECs. Likewise, β cells displayed improved transcriptional, metabolic, and functional maturation. The β cells in VPIOs upregulated maturation markers (MAFA and UCN3) relative to non-vascularized pancreatic islet organoids (PIOs), though still well below primary β cells. Mitochondrial maturation and enhanced respiration were also observed. Notably, VPIOs outperformed non-vascularized PIOs in glucose-stimulated insulin secretion assays. This augmentation of cell identity reflects endothelial-endocrine crosstalk enabled by vascularization. β cells are known to secrete VEGF during islet vascular development.[7] VEGF-VEGFR signaling was also enriched in EC-β cell crosstalk within VPIOs, and adding VEGF to the medium boosted EC fenestration. How endogenous VEGF expression is triggered and spatiotemporally regulated warrants further investigation. In turn, the vascular cells provided niche signals that supported β cell maturation. What shapes organotypic vasculature and islet maturation, and how mural cells, paracrine signals, and extracellular matrix contribute, remain open questions. Together, the reciprocal crosstalk enhances the phenotypes of both cell types.

These vascularized organoids also serve as a model of human islet biology *in vitro*. Wang et al. highlighted this by testing VPIOs under hypoxic and endoplasmic reticulum (ER) stress to mimic an environment that sc-islets may experience following transplantation and prior to anastomosis with the host vascular system. VPIOs exhibited enhanced resilience and a significant reduction in β cell death under low (1%) oxygen and ER stress relative to non-vascularized PIOs, demonstrating

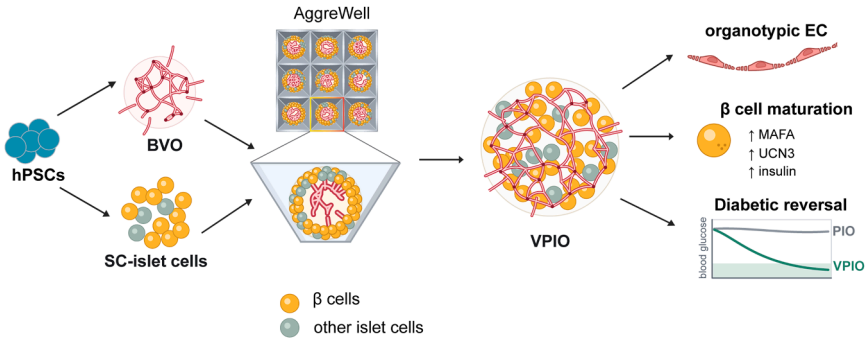


Figure 1. Generating vascularized pancreatic islet organoids from human pluripotent stem cells

Human pluripotent stem cells (hPSCs) are differentiated in parallel into blood vessel organoids (BVOs) and stem cell-derived islet (sc-islet) cells. The two are combined in AggreWell plates, where the sc-islet cells integrate with the BVOs to form vascularized pancreatic islet organoids (VPIOs). VPIOs develop organotypic, fenestrated endothelial cells (ECs) and enhanced β cell maturation, and, upon transplantation into diabetic mice, reverse hyperglycemia more effectively than non-vascularized pancreatic islet organoids (PIOs). Created with BioRender.

that vascular cells support β cell survival. Mechanistically, BMP4 secreted by ECs and fibroblasts was identified as the main factor protecting the β cells, consistent with a recent study.[8] However, this focus on BMP4 alone likely oversimplifies a more complex crosstalk. Even so, VPIOs provide a model to study the intricate communication between islets and their vasculature, and how different signals help induce and maintain tissue-specific identities.

In vivo, VPIOs demonstrated the benefits of organoid pre-vascularization. The authors transplanted VPIOs subcutaneously into immunodeficient mice, reversing diabetes more efficiently than PIOs alone or a mix of BVOs and PIOs delivered without prior co-culture, highlighting the impact of vascular pre-integration. Increased β cell viability in the VPIO grafts underscored the role of vascularization in β cell survival during the early stages of engraftment. Collectively, VPIOs performed similarly to primary human islets in glucose tolerance tests (GTTs) and in circulating human C-peptide levels. Within the grafts, human vessels integrated and anastomosed with the host vasculature, establishing perfusion. Given the hundreds of millions to billions of cells and high manufacturing costs of clinical therapies,[9] such gains in sc-islet efficacy could translate into meaningful cost savings for patients. Realizing that potential will require further development, including a GMP-compliant matrix to replace Matrigel, follow-up beyond the current two months, and validation in an immune-competent setting. Further, the complexity of this co-culture system introduces new manufacturing challenges that would prevent translation into clinical settings; using the knowledge from this study to design a product that can deliver functional and rapidly vascularized islets without extended complex cell culture will be the next challenge in this field.

This work is more than proof of principle: it gives the field both a vascularized islet built entirely from stem cells and a versatile platform to study islet-vascular biology. A natural next step would be to place VPIOs in a perfusable culture system, where extended culture, together with immune or other supporting cells, could support the long-term study of islet development, T1D pathogenesis, and drug responses *in vitro*. *In vivo*, the same pre-vascularization that improved engraftment here points toward safer and more cell-efficient T1D therapy. This strategy builds the vascular niche into the islet from the start, bringing functional, self-vascularizing islets within closer reach of both the laboratory and the clinic.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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