

## Spotlight

# Pancreatic islets in bed with microvasculature—companions for life

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## SUMMARY

In *Cell Stem Cell*, Aghazadeh et al.<sup>1</sup> show that human embryonic stem cell-derived pancreatic progenitors can reverse hyperglycemia for several weeks in streptozotocin-induced diabetic mice when co-transplanted with microvessel fragments into the subcutaneous space.

Type 1 diabetes has emerged as a prime candidate for cellular therapy based on the capacity of pancreatic islets to function as micro-organs outside of the native pancreatic tissue structure. A few milliliters of purified islets isolated from the pancreases of donors can be administered into the portal vein of an immunosuppressed recipient to reverse diabetes for at least 2 years in most recipients.<sup>2,3</sup> Islets provide fine-tuned control over blood glucose levels that remains unmatched by state-of-the-art artificial pancreas systems.<sup>4</sup>

Access to this life-changing therapy remains limited by donor islet supply and the need for lifelong immunosuppression. The combination of stem cell sources and cell cloaking, either through genome engineering or encapsulation devices,<sup>5</sup> may help overcome these hurdles, but achieving robust and long-lasting function of the implanted cells remains a challenge. The liver may not be optimal for islet survival because a large fraction<sup>6</sup> of the islets are lost in the first week(s) post-transplant due to the immediate blood-mediated inflammatory reaction and ischemia-reperfusion injury. The vascular densities achieved after islet revascularization in the liver are insufficient to reach the arterial oxygen levels seen in the native pancreas and required for optimal function of the metabolically demanding islets. The subcutaneous implant site is particularly attractive for ease of access and graft retrievability

but presents even greater challenges for obtaining sufficient graft vascularization for adequate oxygen and nutrient delivery and brisk insulin distribution. Therefore, considerable efforts are underway to improve islet engraftment strategies.

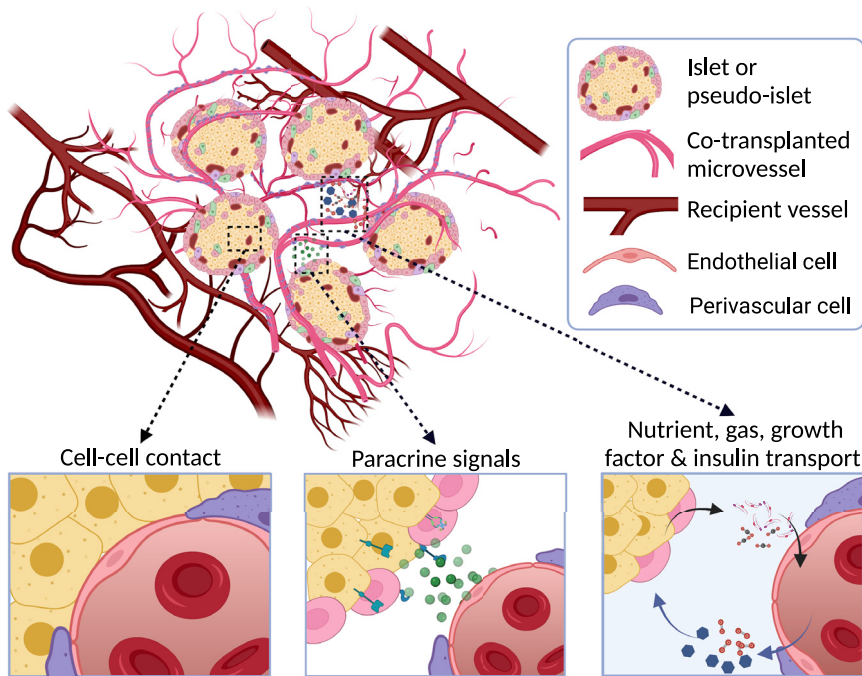
Taking into consideration the role of vasculature in instructing islet development<sup>7</sup> and supporting mature islet function,<sup>8</sup> Aghazadeh et al.<sup>1</sup> show that the subcutaneous site can be rendered hospitable for transplanted islets through incorporation of adipose-derived microvessels—small vascular fragments which can be purified after partial digestion and sieving of adipose tissue. Microvessel fragments retain most of the architecture, cell-cell contacts, and extracellular matrix components of native microvessels, which accelerates the formation of functional interconnected networks after transplantation.<sup>9</sup> Perivascular cells retained during microvessel isolation stabilize the vascular networks formed. In the presence of islets, which produce angiogenic signals (especially in hypoxic conditions), the networks created can improve islet survival and oxygenation and offer a route for insulin transfer into the circulation.

Co-transplants of pancreatic progenitors with microvessel fragments lowered blood glucose levels in streptozotocin-induced diabetic mice. As exogenous insulin levels provided by insulin pellets receded, a modest and transient reduction in blood glucose levels was observed

with pancreatic progenitor aggregates alone or with dispersed endothelial cells. Conversely, the group receiving pancreatic progenitors with microvessel fragments achieved a persistent reduction in fasting blood glucose levels and better glucose tolerance. When fluorophore-labeled dextran was introduced into the circulation, distinct vessels were observed within and around islet-microvessel co-transplants, and red blood cells were observed within vessels. Together, these observations indicate that microvessel fragments inosculate with the recipient vasculature to more effectively irrigate and support the function of the implanted pancreatic progenitors. While others have reported diabetes reversal in rodents with pancreatic progenitors alone even in the subcutaneous space, these new observations suggest that marginal pancreatic progenitor (or islet) mass or quality may be rescued by improved vascularization.

Co-transplantation with microvessel fragments led to higher beta cell mass, increased proliferation, reduced apoptosis and hypoxia marker expression within grafts, and immunoreactivity for nuclear MAFA, a marker of mature beta cells. The results point toward a significant improvement in pancreatic progenitor survival and oxygenation in the days following implantation via the addition of microvessel fragments. The sustained contact with vasculature appears not to affect the specification of these





**Figure 1. Teasing apart the interactions between microvessels and transplanted pancreatic progenitor cell aggregates, which can differentiate to form pseudo-islets.**

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progenitors toward the beta cell lineage but may promote the differentiation of immature beta cells into more mature phenotypes.

Several interrelated effects may thus contribute to the improved function of the pancreatic progenitor grafts (Figure 1):

- (1) Direct contacts: In the native pancreas, most beta cells contact capillaries, with structural and functional polarization.<sup>10</sup> Direct cell-cell contacts between pancreatic progenitors and endothelial/perivascular cells from the microvessel fragments may provide survival and differentiation signals as well as functional support. Extracellular matrix components from the microvessels can affect pancreatic progenitor cell fate decisions through surface receptor binding and biomechanical signals.
- (2) Paracrine effects: Factors secreted by endothelium exert profound effects on pancreas development. Beta cells secrete angiogenic factors. This may create a positive feedback loop

whereby microvessels drive pancreatic progenitor cell differentiation and/or beta cell maturation and function.

- (3) Nutrient/oxygen, growth factor, and insulin transport: Beta cell development is affected by oxygen tension. Oxygen and other nutrients are required for beta cell survival and function. Intraislet endothelial cells are highly fenestrated to facilitate insulin and other endocrine hormone transport from the islet.

From a translational standpoint, autologous microvessel fragments could be sourced from people with diabetes prior to stem cell-derived transplants. However, the logistics would be quite complex, whereby microvessels would be isolated from eventual recipients and undergo quality assurance prior to transplants. Even with cryopreservation, autologous microvessel and allogeneic progenitor cell sourcing would have to be highly coordinated by clinical and/or private entities. Financial and logistic challenges could potentially be addressed by creating microvessel-like structures

*in vitro* from the same stem cell source as the pancreatic cells, but this would still entail strategies to avoid rejection while assuring graft safety, such as through genetic engineering or engineered devices.

Challenges aside, the work presented by Aghazadeh et al.<sup>1</sup> highlights the importance of creating a welcoming vascular bed to reduce early graft losses and sustain long-term function of transplanted cells or reconstructed tissues. One hundred years after the discovery of insulin, a durable, effective cell-based therapy for diabetes appears in reach.

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#### DECLARATION OF INTERESTS

Related to the content, C.A.H. and T.J.K. have received funding and/or research contracts, or consulted for, STEMCELL Technologies, Aspect Biosystems, Sigilon, ViaCyte, and CRISPR Therapeutics. The authors have also filed/granted IP on topic of cell therapy for diabetes. At the time of writing, T.J.K. was employed by ViaCyte.

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