Engineering transferrable microvascular meshes for subcutaneous islet transplantation

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The success of engineered cell or tissue implants is dependent on vascular regeneration to meet adequate metabolic requirements. However, development of a broadly applicable strategy for stable and functional vascularization has remained challenging. We report here highly organized and resilient microvascular meshes fabricated through a controllable anchored self-assembly method. The microvascular meshes are scalable to centimeters, almost free of defects and transferrable to diverse substrates, ready for transplantation. They promote formation of functional blood vessels, with a density as high as ~220 vessels mm⁻², in the poorly vascularized subcutaneous space of SCID-Beige mice. We further demonstrate the feasibility of fabricating microvascular meshes from human induced pluripotent stem cell-derived endothelial cells, opening a way to engineer patient-specific microvasculature. As a proof-of-concept for type 1 diabetes treatment, we combine microvascular meshes and subcutaneously transplanted rat islets and achieve correction of chemically induced diabetes in SCID-Beige mice for 3 months.

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vascular structure in a controlled manner, we developed an ASA strategy. The key to the ASA is a cell organization process on the micropillar substrate where the inner micropillars serve as a geometric template to guide the cell organization into long-range ordering and the boundary micropillars play an anti-contraction effect to prevent the shrinkage of the mesh structure, leading to a stable and ordered microvascular mesh (Fig. 1b). We found that HUVECs, together with a fibrin matrix, self-assembled into an almost defect-free square mesh after 2 days of culture on the micropillar substrate (Fig. 1c). In contrast, HUVEC structures remained random when cultured on a smooth substrate without micropillars (Supplementary Fig. 1). By adjusting the size and arrangement of micropillars, we could precisely control the mesh geometry and dimension. We illustrated simple geometries such as square, pentagon, hexagon, and octagon (Supplementary Fig. 2a) as well as complex structures that resembled spoke, spider web, and natural capillary bed (Supplementary Fig. 2b). Using square network as an example, we also showed that the diameter of fibrin-filled tubular structure could be controlled from approximately 15 to 133 μm, the size of mesh opening from 135 μm to 467 μm, and density from 2 to 44 openings mm⁻² (Supplementary Fig. 2c and Supplementary Table 1).

The ASA approach is scalable and the microvascular meshes can be lifted from the micropillar substrate for transferring. We were able to fabricate a 5 × 5 cm, free-standing, square mesh from HUVECs (Fig. 1d and Supplemental Movie 1). The meshes were stable and cells were viable on micropillar substrate for at least 4 weeks (Supplementary Fig. 3a, b) but rapidly generated sprouts after being transferred and embedded in a fibrin matrix (Fig. 1e and Supplementary Fig. 3c). The meshes promoted dense, functional vascularization on a diffusion chamber after 2 weeks of subcutaneous implantation in SCID-Beige mice (Fig. 1f).

Blood-perfused vessels maintained square-like network with numerous newly formed sprouts, similar to angiogenic sprouting in vitro. It should be noted that microvascular meshes were constantly re-molded during the development of vascularization and anastomoses, and therefore the original shapes of mesh network were not always preserved.

### Simulation and characterization of the microvascular meshes.

To better understand the ASA process, we performed a finite element simulation of the cellular assembling process and further characterization of the microvascular mesh. The simulation, which considers the contractile action of the cells on the fibrin matrix, generated an in-plane displacement contour plot of organized mesh structure (Fig. 2a) and stress and strain distribution (Fig. 2b and Supplementary Fig. 4) on the micropillar substrate. The assembling cells and matrix gradually stopped being in contact with the inner micropillars, and finally only the boundary micropillars were in contact with cells and supported the entire mesh structure (Fig. 2a). The cells and matrix close to boundary micropillars sustained contraction from one direction, while those away from the boundary experienced contraction from all directions, and exhibited higher stresses in the contracted region than in the junction region along both the X (Cauchy stress component 11 in Fig. 2b) and Y (Cauchy stress component 22 in Supplementary Fig. 4a) directions.

Interestingly, cross-sectional images showed that indeed the microvascular meshes were tightened and suspended between micropillars rather than settling at the bottom (Fig. 2c), consistent with the simulation results. Scanning electron microscopic (SEM) images (Fig. 2d and Supplementary Fig. 5) also confirmed that the HUVEC mesh hung among inner micropillars with more contracted regions between junctions and the whole mesh was prevented from shrinking by boundary micropillars. Control
experiments further supported that the formation of a stable cell construct is not through a simple space-filling mechanism alone but highly relying on the micropillars. For example, when HUVEC/fibrin mixture was introduced into grooves with different shapes (e.g., linear, triangle, cross, and windmill) without micropillars inside, cell/fibrin mixture formed structures that were only temporarily stable and all shrank into clumps within 48 h (Supplementary Figs. 6a and 7a) due to intrinsic cellular contraction. In contrast, when micropillars were present inside, cells self-organized into different structures that corresponded to the shapes of the grooves (Supplementary Figs. 6b and 7b).

Confocal images showed that the HUVEC mesh (approximately 25 μm thick after 2 days of culture) had continuous and interconnected tubular structures (Fig. 2e and Supplementary Fig. 8a) in both contracted and junction regions. Further staining showed that the interior of the tubular structure was filled with fibrin on which HUVECs coalesced and adhered (Supplementary Fig. 8b). This self-assembled, cell/fibrin composite structure was consistent with earlier reports and resembled the de novo formation of primitive vasculatures that also involves coalescence of endothelial progenitor cells and subsequent lumen formation. Another important characteristic of the ASA-enabled microvascular meshes is their mechanical robustness. The meshes were elastic and resilient; they even withstood poking with a 6-μm glass pipette. As shown in Fig. 2f and Supplemental Movie 2, the mesh was displaced approximately 150 μm without any visible damage and then recovered to its original position when the pipette was withdrawn. This remarkable mechanical property allowed us to manipulate and transfer the mesh to...
different substrates (Supplementary Fig. 9) without affecting the integrity and fibrin-filled tubular structures of the mesh (Supplementary Fig. 10).

Enhanced vascularization of subcutaneous devices in SCID-Beige mice. To quantitatively investigate how microvascular meshes enhanced vascularization, we compared HUVEC meshes with random HUVEC/fibrin mixture. In both cases, normal human dermal fibroblasts (NHDFs) were added (HUVECs: NHDFs = 9:1) to support and enhance vessel formation. Microvascular meshes or random cell mixture were attached to diffusion chambers using a fibrin gel (Mesh device (n = 8) and Random device (n = 6); Fig. 3a, b; details in Methods and Supplementary Fig. 11). Devices without any cells (No cell device (n = 6)) were used as an additional control. All devices were then implanted into subcutaneous space of SCID-Beige mice. The subcutaneous space is a poorly vascularized site but has many advantages for cell replacement therapies including relatively easy accessibility, minimal invasiveness, and potentially high transplant capacity.

The devices were retrieved, and vascularization was compared after 2 weeks of implantation. Histological hematoxylin/eosin (H&E) staining (Fig. 3c) and quantification of blood vessels (Fig. 3d) surrounding the chambers revealed a significantly higher vascularization in the Mesh device, compared to the No cell and Random devices. These vasculatures were covered by perivascular cells (PVCs) as indicated by smooth muscle actin (α-SMA) staining (Supplementary Fig. 12). Interestingly, positive immunostainings for both human CD31 (Fig. 3e; red) and mouse CD31 (Fig. 3f; green) seemed to suggest that newly formed vessels (in both Random and Mesh devices) were chimeric in nature, indicating the occurrence of anastomoses and vascular remodeling during vascularization. To further demonstrate that generated vessels were functionally connected with mouse vasculature and to confirm the presence of anastomoses, we perfused mice with the Mesh devices through tail vein injections using two lectins. The first lectin was a green fluorescent *Griffonia simplicifolia* lectin I (UES-I) lectin that specifically bound to human ECs and the second one was a red *Ulex europaeus* Agglutinin I (UEA-I) lectin that specifically bound to mouse ECs. The overlap of human- and mouse-specific lectin binding (Fig. 3f) supported that HUVEC mesh promoted not only neovascularization but also anastomoses. In addition, to evaluate the earliest time point that blood-perfused human vasculatures were formed and anastomosed with mouse vascular system, we subcutaneously implanted microvascular meshes of HUVEC-GFP/NHDF (9:1, Mesh device) and random mixture of HUVEC-GFP/NHDF (9:1, Random device) and perfused lipophilic carbocyanine dye Dil into mouse vascular system at different time points (Days 4, 7, and 10, Supplementary Fig. 13 and Fig. 3g). At Day 10, in Mesh device, we found that human vasculatures were functional and connected with mouse vascular system since green color of HUVEC-GFP overlapped with red color of perfused dye Dil. However, in Random device, we did not observe the formation of blood-perfused human vessels under the confocal microscope (Supplementary Fig. 13a). The image analysis showed that the percentage of blood-perfused human vasculatures was 50.4 ± 15.6% (n = 5; mean ± SEM) in Mesh devices (Supplementary Fig. 13b). Furthermore, histological slides of retrieved Random and Mesh devices were stained with human CD31 and α-SMA antibodies. The vasculatures covered by PVCs were identified by vessel cross-sections, which had luminal shape (with erythrocytes inside) and were positively stained by both human CD31 and α-SMA antibodies (Fig. 3h). The percentage of PVC coverage was 19 ± 9% (n = 3) in Random device and 65 ± 6% (n = 6) in Mesh device (Fig. 3i). All the results, taken together, substantiate that ASA-enabled, transferrable microvascular meshes have potential use for vascularization of cell delivery devices.

Correction of diabetes in SCID-Beige mice using rat islets. We next investigated whether microvascular meshes could be used to improve cell replacement therapy for T1D. We loaded rat islets in
diffusion chambers (Fig. 4a; more details in Methods and Supplementary Fig. 14), attached microvascular meshes (HUVECs: NHDFs = 9:1) to the chambers using a fibrin gel (Mesh device), and transplanted the constructs subcutaneously in SCID-Beige mice with STZ-induced diabetes. The chamber had an open structure with pore size ~70 μm, smaller than the average islet size (~150 μm). Each device contained ~500 islet equivalents (IEQ). To better visualize islets, we loaded green fluorescent protein (GFP) rat islets in two Mesh devices (Fig. 4a). Devices encapsulating similar number of islets but with random HUVECs/NHDFs (Random device) or without any HUVECs/NHDFs (No cell device) were used as controls. After transplantation, non-fasting blood glucose (BG) concentration decreased in some mice (No cell device) were used as controls. After transplantation, non-fasting blood glucose (BG) concentration decreased in some mice (No cell Random Mesh) to blood vessels with erythrocytes inside. Density and area percentage of blood vessels at the interface between the device and panniculus carnosus muscle. n = 6 in the No cell and Random, and n = 8 in Mesh groups. Data are mean ± SEM; **P < 0.01, ***P < 0.001, NS (P > 0.05) no significant difference. One-way analysis of variance. Cross-sectional immunostaining images of mature human vasculatures covered by human (UEA-I, green) and mouse (GSL-I, red) endothelial cells, confirming the anastomoses between human and mouse vessels. Blood-perfused human vasculatures anastomosed with mouse vascular system in Mesh device after 10 days of subcutaneous implantation. HUVEC-GFP is green and perfused dye Dil in vessels is red. Representative immunostaining images of mature human vasculatures covered by human CD31 antibody is green) covered with perivascular cells (α-SMA antibody is red) in retrieved Random and Mesh device after 10 days of subcutaneous implantation. The percentage of perivascular cell (PVC) coverage is 19 ± 9% (n = 3; mean ± SEM) and 65 ± 6% (n = 6) for the Random and Mesh devices, respectively. **P < 0.01. Unpaired two-tailed t test.

Fig. 3 Enhancement of vascularization and anastomoses in subcutaneous space of SCID-Beige mice. a Schematics and a digital photo of a Mesh device, which is a diffusion chamber with HUVEC meshes (~25 μm thick, purple) in the fibrin gel (gray) on the top and bottom. The diffusion chamber is a cylindrical cell container with a PDMS ring (blue) as the wall and two nylon grids (green) as the top and bottom. b Fluorescent images of randomly mixed cells (top) and microvascular mesh (bottom) placed on diffusion chambers after 2 days of culture in EGM-2 medium. HUVEC-NHDF = 9:1, Human CD31 antibody is green to show HUVEC, α-smooth muscle actin (α-SMA) antibody is red to show NHDF, and nylon grid is blue. c Cross-sectional hematoxylin/eosin staining images of retrieved devices after 14 days of implantation. Yellow arrowheads point to blood vessels with erythrocytes inside. d Density and area percentage of blood vessels at the interface between the device and panniculus carnosus muscle. n = 6 in the No cell and Random, and n = 8 in Mesh groups. Data are mean ± SEM; **P < 0.01, ***P < 0.001, NS (P > 0.05) no significant difference. One-way analysis of variance. e Cross-sectional immunostaining images of human (red) and mouse (green) CD31 antibodies showing the human and mouse blood vessels at the interface between the device and panniculus carnosus muscle. f Confocal images of perfused lectins bound to human (UEA-I, green) and mouse (GSL-I, red) endothelial cells, confirming the anastomoses between human and mouse vessels. g Blood-perfused human vasculatures anastomosed with mouse vascular system in Mesh device after 10 days of subcutaneous implantation. HUVEC-GFP is green and perfused dye Dil in vessels is red. h Representative immunostaining images of mature human vasculatures covered by human CD31 antibody is green) covered with perivascular cells (α-SMA antibody is red) in retrieved Random and Mesh device after 10 days of subcutaneous implantation. i The percentage of perivascular cell (PVC) coverage is 19 ± 9% (n = 3; mean ± SEM) and 65 ± 6% (n = 6) for the Random and Mesh devices, respectively. **P < 0.01. Unpaired two-tailed t test.
mice had a small number and were all normoglycemic, IPGTT showed no difference between the groups.

The devices retrieved at Day 42 were evaluated histologically for vascularization (Fig. 4d). Although viable islets with normal morphology were found in all the three groups, islets in transplants from the Mesh group were preferred by significantly more blood vessels than the two control groups, consistent with the diabetes correction results (Fig. 4b). Although NHDFs were incorporated with iPSC-ECs to promote the maturation of functional vessels, we still noticed that a few erythrocytes leaked out of immature vessels (hemorrhage) in histological staining. To further improve the maturation of newly formed vessels, mesenchymal stem cells could be used as supporting cells. Additional immunostaining (Fig. 4e) confirmed that islets in the Mesh group were functional with positive insulin staining and were also highly vascularized (CD31 staining) both externally and internally. Similar to the results with empty devices (no islet, Fig. 3e, f), positive overlapping staining with both human and mouse CD31 antibodies demonstrated anastomoses between human and mouse vessels (Fig. 4f). Moreover, to better visualize the connection between vessels inside rat islets and surrounding mouse vessels in mice from the Mesh group, we performed whole-mouse perfusions, prior to retrieval at Day 42, Day 91, and Day 112, with a fluorescent lipophilic carbocyanine dye DiI. Confocal and fluorescent images of the perfused devices clearly showed interconnected, 3D structure of vascular networks in transplanted islets (Fig. 4g, Supplementary Fig. 15, and Supplemental Movie 3 for the device from Day 42 retrieval and Fig. 4h for the device with GFP rat islets from Day 91 and Day 112 retrievals). Together, these results confirmed the effectiveness of transferrable microvascular meshes in promoting revascularization of donor islets and maintaining normoglycemia for up to 3 months in diabetic mice.

Microvascular meshes from human iPSC-ECs. To explore whether the ASA strategy was applicable to other types of ECs and would be potentially used in a clinical setting, we tested human iPSC-ECs. iPSC-ECs have been considered as an autologous, unlimited cell source for vascularization and therefore have great potential for clinical applications. Similar to HUVECs, iPSC-ECs formed various controllable microvascular meshes with fibrin-filled tubular structures on micropillar substrates (Fig. 5a–c). The different geometrical meshes can be transferred
to diffusion chambers (Supplementary Fig. 16). To evaluate the ability to enhance vascularization, microvascular meshes of square shape were implanted in subcutaneous space of SCID-Beige mice for 2 weeks. In all in vivo experiments, a small amount of NHDFs were mixed with iPSC-ECs (iPSC-EC:NHDF = 9:1). As shown in Fig. 5d, H&E staining and immunostaining (CD31 and α-SMA) revealed vasculatures covered by PVCs at the interface between the device and panniculus carnosus muscle for all the three groups. However, the Mesh devices (n = 5) resulted in significantly more blood vessels in terms of both density and area percentage than the No cell (n = 5) and Random (n = 5) devices (Fig. 5e). Moreover, the formation of blood-perfused iPSC-EC vessels was observed on Day 10 posttransplantation, and the percentage of blood-perfused iPSC-EC-derived human vasculatures was 47.0 ± 20.3% (n = 3). (Supplementary Fig. 17). Positive staining of human and mouse CD31 antibodies confirmed the anastomoses (Fig. 5f).

The iPSC-EC mesh was attached to a diffusion chamber containing rat islets using a fibrin gel (Mesh iPSC-EC (n = 6); Fig. 6a) similar to HUVEC mesh. The Mesh group led to significantly better diabetes correction than the control groups (No iPSC-EC (n = 5) and Random iPSC-EC (n = 6)) in the rat-to-mouse transplantation model (Fig. 6b and Supplementary Table 3). Mice from the Mesh group also responded to IPGTTs, performed on Day 30 and Day 90, significantly better than those from control groups (Fig. 6c). Compared to normal mice, the glucose response of mice in Mesh group was delayed. In the future, enhancing the function and vascularization of iPSC-EC mesh might help transplanted islets realize improved BG control and glucose responsiveness in IPGTT. Immunostaining of the retrieved Mesh devices confirmed that iPSC-EC meshes promoted anastomoses between human and mouse vessels (Fig. 6d). Whole-mouse perfusion prior to retrieval and confocal imaging showed that the transplanted rat islets were functionally re-vascularized (Fig. 6e and Supplemental Movie 4). Re-vascularization and insulin secretion by the islets were verified by H&E (Fig. 6f) and immunostaining (Fig. 6g). Blood-perfused vessels were present both inside and outside the islets (H&E image), and the islets were positive for both insulin and CD31 staining. These results demonstrate the feasibility of engineering patient-specific microvascular meshes from iPSC-ECs and the potential use in cell replacement therapies for T1D.

**Discussion**

We utilize spatially arranged micropillars to fabricate high-resolution, resilient, and transferrable microvascular meshes. Micropillars play two roles in the ASA: guiding the ECs to form patterns with controllable geometry and preventing the cells and matrix from shrinking. Compared to random EC tubes formed on a smooth substrate, the ASA-enabled microvascular meshes are continuous, interconnected, and precisely controlled. In a poorly vascularized subcutaneous space, microvascular meshes promote more efficient vascularization and anastomoses with host vasculature than randomly mixed cells. Subcutaneous space is an attractive transplant site due to its easy accessibility and relatively large capacity for transplantation; however, subcutaneous space has much less vasculature compared to other vascularized sites, such as small bowel mesentery, omentum, and epididymal fat pad. In Random device, cells were homogeneously dispersed inside the fibrin gel on top and bottom of the diffusion chamber and required time to form interconnected...
network. In contrast, microvascular meshes provide a pre-formed, highly interconnected network for secretion of angiogenic factors and generation of vascular sprouts. The hierarchical structures of pre-formed mesh network and newly branched sprouts efficiently induce ingrowth and anastomoses of host vasculature. Likely due to such multilevel configuration, microvascular meshes resulted in a high vasculature density. Our results demonstrated that endothelial cord of 500 μm diameter resulted in vessel size of ~50 mm and the network structure significantly shrunk and failed cells. Therefore, great efforts have been made to find an alternative islet transplantation strategy that is less invasive, and this strategy includes use of microvascular meshes.

The microvascular mesh although thin is within the same size range of capillary in vivo (~5–40 μm) and the network structure mimics the capillary bed in vivo and is able to enhance vascularization. The work by Chen’s group also showed that thin vascular structures (i.e., ~50 μm endothelial cell cords) could enhance vascularization. Furthermore, even thicker vascular-like structures fabricated in vitro would significantly shrink and generate thin vasculatures in vivo. For example, it was found that endothelial cord of 500 μm diameter resulted in vessel size of ~15 μm in vivo. We speculate that these thick cellular structures were unstable and not completely contracted in vitro, which caused dramatical size shrinkage in vivo. Interestingly, although the thickness of our microvascular mesh was thin in vitro, the size remained similar upon transplantation based on the observation of the blood-perfused human vasculatures in mice. This might be the result of more complete cellular contraction from our unique fabrication method.

The resilient and transferrable microvascular meshes that we described in this work made it possible to vascularize islets subcutaneously transplanted in retrievable delivery devices. Cell replacement therapy such as intrahepatic transplantation of donor islets is relatively successful in some patients. However, there are a number of limitations, including immediate blood-mediated inflammatory response, potential risks of thrombosis and localized steatosis, and inability to retrieve or replace failed cells. Therefore, great efforts have been made to find an alternative islet transplantation strategy that is less invasive,
supports long-term cell function, and allows cell retrieval or replacement. Previous studies have shown that rat islets subcutaneously transplanted in immunodeficient mice maintained short-term normoglycemia (~20–28 days) at the low dose (~375–750 islets or IEQ), but the long-term islet function was not presented. We demonstrated that the microvascular meshes significantly improved the function of rat islets (approximate 500 IEQ) in the poorly vascularized but convenient subcutaneous space and enabled diabetes correction in SCID-Beige mice for up to 3 months. Importantly, given that microvascular meshes may be made from autologous cells such as iPSC-ECs and can be transferred to different delivery or immuno-protective devices, our approach may contribute to an immunosuppression-free cell replacement therapy for T1D.

The scalability is an important requirement for cell replacement therapies and has been challenging for subcutaneous devices. ASA-enabled microvascular meshes can be fabricated in larger sizes (i.e. ~25 cm²) and stacked with alternating devices in the Z direction for scale up (Supplementary Fig. 18a, b). High level of vascularization was observed in microvascular meshes (Supplementary Fig. 18c, d), and the vessel density is similar between the top layer and middle layer (Supplementary Fig. 18d). In the middle layer, blood-perfused human vasculatures were formed (Supplementary Fig. 18e), rat islets remained viable (Supplementary Fig. 18f), and the intra-islet vasculatures could be perfused (Supplementary Fig. 18g) after 2 weeks of transplantation. Given that different types of ECs may be isolated from the body, fragmented, patient- and tissue/organ-specific microvascular meshes could be created using the ASA. In this work, we only demonstrated one line of iPSC-EC, but in principle different iPSC-EC lines could be organized into microvascular meshes to explore the broader applicability of ASA-enabled cell self-assembly and vascularization. Moreover, microvascular meshes may be combined with other cell types such as hepatocytes and cardiomyocytes for liver and cardiovascular engineering applications or fibroblasts and smooth muscle cells to assist wound healing. Lastly, the ASA as a general approach may be expanded to other bioengineering fields to construct geometrically defined, high-resolution live materials at micro-scales or to organize therapeutic cells into specific patterns for diverse applications.

Methods

Fabrication of micropillar substrate. The micropillar substrate was composed of polydimethylsiloxane (PDMS) and fabricated using standard soft lithography at the Cornell NanoScale Facility. Briefly, a photomask was prepared using a mask writer (DNL2000, Heidelberg Instruments). The silicon wafer was spin-coated with SU-8 (Dow Corning) micropillars. A mixture (10:1, v:v) of Sylgard 184 silicone elastomer components was casted onto the master wafer. Stacked micropillars were used to create PDMS (Sylgard 184, Dow Corning) micropillars. A mixture (10:1, v:v) of Sylgard 184 silicone elastomer components was casted onto the master wafer, cured at ~60 °C overnight, and peeled off from the master to obtain a PDMS micropillar substrate.

Cell culture. Normal HUVECs (passages 4–6, Lonza) or HUVECs expressing GFP (passages 4–10, Lonza) were cultured in fibroblast growth factor-2 (FGF-2) medium (Lonza). NHDFs were cultured in fibroblast growth factor-2 (FGF-2) medium (Lonza). Cells were cultured in Endothelial Cell Growth Medium-2 (EGM-2) (Lonza). Cells were plated at a density of ~10,000 cells cm⁻². They were cultured in EGM-2 medium. Bone morphogenetic protein-4 (R&D Systems) (Days 0–4), and 8 ng mL⁻¹ FGF-2 (Peprotech) (Days 2–14). On Day 4, embryonic bodies were transferred to adherent conditions on Matrigel (BD Biosciences) coated plates and medium was supplemented with 25 ng mL⁻¹ vascular endothelial growth factor-A (Peprotech) (Days 4–14), 10 µM SB431542 (Tocris) (Day 7–remainder of experiment). After 14 days, cell mixtures were dissociated using Accutase (eBioscience) and sorted for CD31⁺ endothelial cells. Purified iPSC-ECs were cultured in EGM-2 medium for further experiment.

Formation of microvascular meshes by ASA. PDMS micropillar substrates were autoclaved, treated with UV ozone cleaner (Model 18, Jelight) for 10 min, placed in a 24-well plate, and coated with 1% (w/v) Pluronic F127 (Sigma) solution before cell seeding to prevent cell attachment on PDMS surface and to facilitate cell assembly. Form microvascular meshes (Supplementary Fig. 11), cells were suspended in fibrinogen solution (3 mg mL⁻¹ fibrinogen (from bovine plasma, Sigma) and 1.0 U mL⁻¹ thrombin (from bovine plasma, Sigma)) at a concentration of 8.0 x 10⁶ cells mL⁻¹ and poured over a PDMS micropillar substrate. Excess cell suspension was scraped off with a cover glass. The cells in fibrin solution homogeneously filled the interspaces between micropillars. After 15 min of incubation at 37 °C, a fibrin gel was formed and cells embedded inside were cultured in EGM-2 medium. Microvascular meshes formed between micropillars after overnight culture and further stabilized during subsequent 2 days of culture. All the in vitro characterization of microvascular mesh was performed after 2 days of culture. In some experiments, fibrinogen conjugated with Alexa Fluor 488 (Molecular Probes, Cat No. F13191) was mixed with normal fibrinogen to form fluorescent fibrin gel (1:200 dilution).

Simulation. We postulate a free energy that has a passive elastic contribution from the fibrin matrix and an active contractile contribution from the cells, and we consider that they act in parallel. The effects of contractility are assumed to be geometrically non-linear in the contractile matrix as observed in the simulations and in agreement with experimental observations. The effect of pore pressure is neglected, essentially considering the fibrin matrix as a Neo-Hookean compressible foam on which the cells are acting. Both of these assumptions are prevalent in the literature for modeling and simulation of contractile microtissues, adequate for capturing the key features of the response of the composite microtissue. The assumed free energy has the form

\[ U(J) = I_2(J) + \lambda \eta \beta \, \mu \left( \frac{2}{3} \ln J - \frac{1}{2} \ln (\beta \eta) \right) \]

where \( J \) is the third principal invariant of the deformation gradient, \( I_2(J) \) is the second invariant of the deformation gradient, \( \lambda \) is the principal invariant of the deformation gradient, \( \beta \) is the Poisson's ratio, and \( \eta \) is the chemical potential. The parameters are \( \lambda = 1.9 \, \mu \text{N m}^{-2} \), \( \beta = 1.9 \, \mu \text{N m}^{-2} \), and \( \eta = 2 \times 10^6 \, \mu \text{N m}^{-2} \) for the capsular and the post-contraction microtissue.

In the last part of the equation, the first two terms correspond to the compressible Neo-Hookean formulation for the homogenized fibrin network and the last term to the homogenized active contractile action of the cells. Decoupling the energetic contributions is a prevalent assumption in the field of computational models. Considering both the active (cell) and passive (fibrin) parts of the free energy, the critical in the prediction of the aggregate response of the composite microtissue. Where \( I_c \) is the first principal invariant of the right Cauchy–Green deformation gradient \( C_{ij} = F_{ij} F_{kj} \), \( J = \det(\boldsymbol{F}) \) is the determinant of the deformation gradient \( \boldsymbol{F} \) and \( \beta \) is the shear modulus of matrix.

The microchannel diameter is 400 µm and pillar-to-pillar distance is 200 µm. Young’s modulus of the matrix is taken to be \( E = 1.9 \, \text{mN µm}^{-2} \) interpolating \( E = 1.9 \, \text{mN µm}^{-2} \) from the results of Ghajare et al. Poisson’s ratio is set at \( \nu = 0.3 \), and the chemo-mechanical stiffness modulus \( \beta = 2 \, \text{mN µm}^{-2} \) was calibrated to the experimental results to match the observed in-plane displacements. The shear modulus of matrix is obtained through \( \mu = \frac{E}{2(1+\nu)} \) and Lame’s first parameter through \( \lambda = \frac{E}{3(1+\nu)} \). The simulations are under plane-strain conditions, consistent with the calibration procedure to obtain the model parameters. A simulation is performed starting from zero activation, ramping up to full activation to study the effect of cell contraction, leading to large deformations to the microtissue as observed in the simulations and in agreement with experimental observations. The units of stress in the results are in mN µm⁻² and displacement units are µm. The strains for this large deformation problem are quantified through the Euler–Lagrange strain tensor defined as \( \varepsilon_{ij} = F_{ij} - I_{ij} \), where \( I \) is the unit second-order tensor.

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Transfer of microvascular meshes. Owing to intrinsic elasticity and resilience, microvascular mesh on micropillar substrate can be manipulated and transferred to different places. The microvascular mesh could float after immersing the micropillar substrate in phosphate-buffered saline (PBS) solution. When a rod was placed beneath the floating microvascular mesh and gently lifted up, the microvascular mesh wraps onto the rod. Alternatively, to transfer a microvascular mesh onto different substrates, a PDMS frame (pre-soaked in 50 g solution) was added to enhance vascularization and function of vasculatures. As previously described, microvascular mesh was assembled in the same way on the micropillar substrate. The parameters of a micropillar substrate were as follows: substrate size was 1 × 1 cm, micropillar diameter and height were 400 and 200 μm, respectively, and micropillar-to-micropillar interval was approximately 200 μm. The void space between microvascular meshes was approximately 1 μL. The total cell number on the micropillar substrate was approximately 1.1 × 10^5. After microvascular mesh was cultured for 2 days on the micropillar substrate, a fibrin solution (6.0 mg mL^−1 fibrinogen and 2.0 U mL^−1 thrombin) was pipetted on top of microvascular mesh and then the chamber was placed in fibrin solution. Another microvascular mesh was placed on a micropillar substrate and was flipped in the fibrin solution, on top of the chamber. After 15 min of incubation at 37 °C, microvascular meshes were embedded in fibrin gel and positioned onto the chamber surface, and the void space created by the removal of micropillars was filled with additional fibrin gel (Mesh device, Supplementary Fig. 11). The Mesh device was left to incubate for 2 medium for approximately 4 h prior to transplantation. For No cell device, a fibrin solution (6.0 mg mL^−1 fibrinogen and 2.0 U mL^−1 thrombin) without cells was settled around the chamber and cultured for 2 days prior to transplantation. For the Random device, a fibrin solution (same volume used for the Mesh device) containing a random mixture of ECs and NHDFs (same cell amount used for making the microvascular mesh) was placed on top of the chamber and gelled at 37 °C. Then the bottom of the chamber was placed with cells in the fibrin matrix in the same way. The Random device was cultured for 2 days prior to transplantation.

SCI-D Beige mice (male and female, model number C57BL/6J, 6–8 weeks old, Taconic, Holliston, MA, USA) were used for confocal microscopy and maintained at the same rate throughout the procedure. Three 2.5 cm^2 squares were shaved (two on one flank and one on the opposite flank of the mouse) and sterilized with alternating scrubs of betadine and 70% (v/v) ethanol. A small droplet of 0.15% Liberase (Research Grade, Roche) in RPMI 1640 (Gibco) was introduced into an 8 mm circular PDMS frame (inner diameter: 7 mm, outer diameter: 6 mm, thickness: 0.6 mm) with nylon grid at the bottom. A second nylon grid was placed on top of the PDMS frame and glued by gelling fibrin at 37 °C for 15 min. A fibrin solution (6.0 mg mL^−1 fibrinogen and 2.0 U mL^−1 thrombin) was pipetted on top of a HUVEC microvascular mesh on a micropillar substrate, which had been cultured for 2 days in EGM-2 medium. The chamber containing rat islets was placed in the fibrin solution, and another HUVEC microvascular mesh on a micropillar substrate was flipped and placed in the fibrin solution, on top of the chamber. After 15 min of incubation at 37 °C, HUVEC microvascular meshes attached on both sides of the chamber and the void space created by the removal of micropillars was filled with additional fibrin gel (Mesh device, Supplementary Fig. 14). For No cell device (n = 9, from 3 isolation and encapsulation experiments), a fibrin solution containing rat islets was loaded into a PDMS frame with a nylon grid at the bottom. Another nylon grid was placed on top of the PDMS frame and glued by gelling fibrin at 37 °C for 15 min. The Random device (n = 11, from 3 isolation and encapsulation experiments) was prepared in the same way as No cell device except the random mixture of ECs and NHDFs in fibrin matrix had been cultured on the nylon grids for 2 days. Subcutaneous transplantation was performed as previously described for the empty device without islets. In iPS-C-EC and rat transplantations, n = 5 in No iPS-C-EC group, n = 6 in Random iPS-C-EC group, and n = 6 in Mesh iPS-C-EC group were from 2 isolation and encapsulation experiments.

Evaluation of hyperglycemia correction in diabetic mice. To create insulin-dependent diabetic mice, healthy SCI-D-Beige mice were treated with freshly prepared STZ solution (120 mg kg^−1 mouse) twice via intraperitoneal injection. BG level of all the mice was retested prior to transplantation. Only mice whose non-fasting BG level was >350 mg dL^−1 were considered diabetic. Mice were randomized among the control and experimental groups to keep BG levels at the similar level for all groups at the beginning of transplantation.

Non-fasting BG levels were monitored twice during the first week and then once a week following the transplant surgery. BG measurements were randomly performed by blinded or non-blinded personnel. A small droplet of blood was collected from the tail vein and glucose concentration was measured with a commercial glucometer (Clarity Plus, Diagnostic Test Group). Mice with non-fasting BG levels <200 mg dL^−1 were considered normoglycemic. After retrieving the devices from diabetic mice, non-fasting BG was monitored for one more week. The retrieved devices were fixed in 10% formalin, embedded in paraffin, and sectioned. H&E staining and immunostaining of the sections were performed.

Mouse blood vessel perfusion. To image anastomoses between mouse and human blood vessels, two types of leucocytes (100 μL each) were injected into mouse through tail vein after 14 days of transplantation. Green fluorescent UEA-1 lectin (2 mg mL^−1) specifically bound to human endothelial cells. Red DiLight 594− labeled SS1-lectin B1 (1 mg mL^−1) specifically bound to mouse endothelial cells. Mice were euthanized, and leucocytes were harvested. Human CD31 was immunocytochemically bound to human endothelial cells6. Red DyLight 594− labeled SS1-lectin B1 (1 mg mL^−1) specifically bound to mouse endothelial cells. Mice were euthanized, and leucocytes were harvested. Human CD31 was immunocytochemically bound to human endothelial cells. Red DyLight 594− labeled SS1-lectin B1 (1 mg mL^−1) specifically bound to mouse endothelial cells. Mice were euthanized, and leucocytes were harvested. Human CD31 was immunocytochemically bound to human endothelial cells.
Devices retrieved from mice were fixed in 10% formalin, processed, embedded, and sectioned for immunohistochemistry. The primary antibodies were rabbit anti-human CD31 (1:200 dilution, Sigma, Cat. No. SAB5060916–100UL), goat anti-mouse CD31 (1:200 dilution, R&D Systems, Cat. No. AF6382), and α-SMA antibody conjugated by Cy3 (1:200 dilution, Sigma, Cat. No. C6198–2 ML). The secondary antibodies were Alexa Fluor® 594 donkey anti-rabbit antibody (1:400 dilution, Invitrogen, Cat. No. R37119), Alexa Fluor® 488 donkey anti-rabbit antibody (1:400 dilution, Invitrogen, Cat. No. R37118), and Alexa Fluor® 488 donkey anti-goat antibody (1:400 dilution, Invitrogen, Cat. No. A-11055). After washing with PBS, the slides were mounted in Fluoroshield® with 4,6-diamidino-2-phenylindole (Sigma) and imaged with a fluorescence microscope (EVOS, AMI).

On H&E staining images, human or mouse blood vessels were identified by luminal structures with erythrocytes inside. The vessel number was quantified by counting individual vessels within the interfacial area between the device and paninculus carnosus muscle. The vessel density (vessels/mm$^2$) was calculated by dividing the total vessel number by the interfacial area. The area percentage of vessels was calculated by dividing the total area of erythrocyte-containing luminal structures by the interfacial area. Blood perfusion on Day 10 was quantified by image analysis (Fiji Image) (https://imagej.net/Fiji)). The percentage of blood-perfused human vessels was calculated by dividing the pixel area of merged green and red color (human vessels containing perfused dye) with the pixel area of green color (total human vessels). Histological slides of retrieved devices (10 days after transplantation) were stained with human CD31 and α-SMA antibodies. The human vasculatures covered with PECs were identified by vessel cross-sections that had luminal shape (with erythrocytes inside) and were positively stained by both human CD31 and α-SMA antibodies. For immunohistochemical detection of rat insulin, histological sections were fixed in 10% formalin, processed, embedded, and sectioned for immunohistochemistry. The primary antibodies were rabbit anti-Nature Communication | https://doi.org/10.1038/s41467-019-12373-5 | www.nature.com/naturecommunications

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Author contributions

W.S. and M.M. conceived experiments and wrote the manuscript. All authors contributed to manuscript revision. W.S. and A.C. conducted experiments. R.E.S. differentiated human induced pluripotent stem cells into endothelial cells, B.L. and N.B. performed simulation of vascular mesh assembly on micropillar substrate. L.-H.W. drew scheme and conducted characterization. D.A. contributed to SEM characterization. S.H.C. performed micropetite poking experiment. J.A.F. contributed to animal experiments. Y.P. contributed to statistical analysis. Q.L. implemented immunostaining. D.T.B. and X.W. prepared materials, cells, and diabetic mice. V.K.L. and G.D. derived and cultured HUVEC-GFP cells for the fabrication of microvascular meshes and the blood perfusion experiments. W.S., A.C., and M.M. analyzed experimental results.

Competing Interests

The authors declare no competing interests.

Additional information

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