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Scalable vascularized implants

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Abstract

Biodegradable and perfusable scaffolds enable the fabrication of implantable, millimetre-scale cardiac and hepatic tissue models.

In tissues, nutrient and oxygen delivery as well as waste removal require an efficient interface between the vascular network and the parenchyma. Vascularization is therefore crucial when engineering tissue constructs for *in vivo* implantation or as *in vitro* organ-on-a-chip models of human diseases^{1,2}. Small three-dimensional microtissues with isolated vascular networks³ and low metabolic demands^{4–5} have been engineered, but the mismatched mechanical and material demands of the vascular and structural tissue components make it difficult to integrate perfusable vasculature within parenchymal tissue. Proper vascularization indeed represents a major challenge for the generation of large-scale, functional tissues. Milica Radisic and colleagues⁶ now report in *Nature Materials* a tissue-design approach that utilizes different scaffold materials for the vessel network and the parenchyma and that allows for extensive permeation and interaction between the two. The approach can generate implantable, fully vascularized cardiac and hepatic tissue models.

Tissues for implantation or for organ-on-a-chip technology require 3D cellular organization, vasculature that is functional (for example, non-thrombogenic, stimuli-responsive and with angiogenic potential), a permissive extracellular environment, and cell–cell interactions. By taking advantage of microfabrication and 3D stamping, Radisic and colleagues generated a biodegradable elastomer ‘AngioChip’ scaffold that incorporated multiple layers of branched microchannel networks (Fig. 1). Channel size and geometry can be changed in each layer of the scaffold and layer-by-layer stamping allowed for the creation of a complex 3D scaffold with branched structures. Around the vascular network, the additional scaffold provided anisotropy in the parenchyma to accurately mimic tissue organization and function. The scaffold had relatively thin vessel walls with tunable rigidity, permitting perfusion through the open lumen over a wide range of physiological pressures. On the vessel walls, microholes and nanopores enhanced permeability and permitted cell migration and efficient molecular exchange with the parenchyma. More importantly, the vascular scaffold maintained robust structural integrity during the extensive matrix remodelling that takes place in long-term culture.

Radisic and co-authors showed that after seeding the scaffold with endothelial cells the vessel walls became endothelialized (Fig. 2) and that biochemical stimulants promoted the endothelial cells to migrate through the microholes into the parenchyma to form new blood vessels, thus emulating sprouting angiogenesis. Notably, the authors applied their fabrication

approach to generate human liver and heart tissue on the millimetre scale by additionally incorporating hepatic or cardiac cells in hydrogels surrounding the vessel scaffold. Liver and heart tissue are highly metabolic, which poses significant demands in terms of perfusion and vascularization. The authors demonstrated that hepatic tissue survived over seven days of culture, maintaining urea secretion and drug metabolism, and that cardiac tissue showed robust cell survival and organization, physiological electrical wave propagation and biochemical excitability. In addition, they indicate that the perfusion is critical to maintain high viability through the thick cardiac tissue. The ability to control perfusion is a big step forward towards engineering large-scale tissues and provides opportunities to better understand the role of perfusion and vasculature in tissue maturation and function. Although cardiac tissue patches with vascular structures have been made previously and have had success *in vivo*⁷, the level of function and perfusion that Radisic and colleagues achieved is unprecedented. Furthermore, they demonstrated direct anastomosis *in vivo*, where the perfusable vascular scaffold allowed for immediate host integration with no blood clots and supported tissue survival for weeks. This represents an important milestone in engineered tissue therapies for heart regeneration.

Further improvements will however be needed before vascularized tissue scaffolds are able to meet all of the requirements needed to replace *in vivo* tissue. For example, the total volume occupied by the vascular walls in the scaffold is much higher than the physiological range and there is no difference in wall thickness and/or structure for the large and small vessels. The degradation kinetics of the wall and its impact on the structure and function of both the parenchyma and the vascular network remains to be assessed. Improvements on the properties of the vessel walls and methods to further control vascular function would broaden the applications of this technology. Furthermore, the ability to modulate muscularization and pericyte coverage of the endothelium to emulate large arteries and small arterioles, respectively, would allow for the generation of hierarchical vascular structures with complex functions, including vasodilation and vasoconstriction. In addition to vascular function, the scaffold needs to be compatible with parenchyma function. For example, electrical coupling between implanted cardiac tissue and the host heart is important for the therapeutic application of cardiac tissue scaffolds. The scaffold developed by Radisic and colleagues should establish the basis for further control of vascular angiogenesis and arteriogenesis, and allow for the fast and accurate recapitulation of complex organs. Further developments of this technology will advance our understanding of complex biological questions concerning tissue-scale biology and vascular-network–parenchyma interactions, and promote the generation of implantable tissues on a therapeutically relevant scale.

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Figure 1. Scaffold structure and prevascularized tissue model. **a**, Scanning electron micrographs of a 2D scaffold and a multi-layer 3D AngioChip scaffold created using the 3D stamping technique (scale bars, 1 mm). **b**, Schematic of the assembly of the bioreactor and of the vascularized tissue. ECM, extracellular matrix. Figure adapted from ref. 6, Nature Publishing Group.

Figure 2. Scaffold endothelialization. **a**, The internal vasculature of an endothelialized AngioChip scaffold revealed by immunostaining of endothelial cells (CD31, red). **b**, Immunostaining of F-actin (green) in the cross-section of endothelialized, thick multi-layer human AngioChip cardiac tissue. Figure reproduced from ref. 6, NPG.