Creating Surgically Relevant de novo Tissue Engineered Constructs Using Biocompatible Biodegradable Polymers

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INTRODUCTION:

The fabrication of surgically relevant, pre-formed vascularized artificial tissue is currently beyond the scope of any tissue engineering approach. Current scaffold based therapeutic strategies are highly fallible as they rely upon host-vessel revascularization of the construct subsequent to implantation. We have previously reported a technique for fabricating constructs utilizing sucrose as a sacrificial fiber to form empty channels (a “capillary bed”) within a larger poly(dimethylsiloxane) (PDMS) shell1. Our current objective is to modify this technique by substituting biocompatible, biodegradable polymers for non-biodegradable PDMS, thereby creating surgically relevant de novo constructs to use in place of autologous tissue for transfer.

MATERIALS AND METHODS:

Various biodegradable polymers were compatibility-tested. Alginate and poly(lactic acid) (PLA) were explored in depth. Alginate 4% w/v was mixed with calcium sulfate 2% w/v in a 2:1 ratio and collagen type I 1% w/v in a 5:1 ratio and injected into a mass of PLA microfibers (diameter 10-100µm). Constructs were fabricated with an internal biodegradable polyglactone mesh structurally reinforcing the inlet and outlet macrochannels to allow for vascular anastomosis. PLA was sacrificed by construct immersion in chloroform. Patency and continuity were evaluated by gadolinium-contrast enhanced µMRI (resolution 117 µm). RGD-modified and unmodified alginate and alginate/collagen (5:1 and 10:1) films were seeded with human umbilical vein endothelial cells (HUVECs) and imaged. A single channel construct was seeded with GFP-tagged endothelial cells and in situ fluorescent imaged 4 days later. Lastly, a construct was anastomosed to explanted 1mm diameter rodent vessels and perfused via perfusion pump.

RESULTS:

Multiple combinations of bulk material and sacrificial fibers were compatible with respect to polarity and solubility. Alginate and collagen type I (bulk) and PLA (sacrificial fiber network) were ultimately selected due to their complementary properties, low cost and availability. Constructs were fabricated in a manner analogous to our sucrose/PDMS technique. Alginate and collagen were unaltered by exposure to chloroform. PLA dissolved completely, leaving a patent network of microchannels within the hydrogel, confluent with inlet and outlet macrochannels as demonstrated by gadolinium contrast-enhanced µMRI. HUVECS adhered most effectively to RGD-modified 5:1 alginate/collagen films. A single-channel construct was effectively seeded with GFP-tagged HUVECs, thereby creating an endothelial cell-lined lumen as demonstrated by in situ fluorescent imaging (Figure 1). Lastly, explanted rat aorta was anastomosed to a construct ex vivo using standard microsurgical techniques. This construct was then perfused via perfusion pump without leakage from the anastomosis between the hydrogel and the vessel.

DISCUSSION AND CONCLUSIONS:

Using our novel sacrificial technique, we have created surgically relevant de novo constructs from biodegradable, biocompatible materials and perfused them in a circuit including biologic vessels. Furthermore, we demonstrated that such constructs could be seeded with endothelial cells, theoretically allowing for long-term in vivo clot free blood flow. Customizable to any size or shape, we believe such constructs may revolutionize the fields of tissue engineering and reconstructive microsurgery.

REFERENCES:


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DISCLOSURES:

The authors have nothing to disclose.