Title: Development of vascular inductive alginate bioinks with defined chemistry for vascularized tissue unit fabrication

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Abstract:

A critical hurdle in the scalability of bioprinting is the need to pre-vascularize printed tissues and organs so that they anastomose with the host blood supply after transplantation. Many recent studies have focused on developing novel fabrication methods for vascular bioprinting, but few have focused on developing bioinks with chemistries tailored specifically for inducing vascular network formation. Here we developed a vascular inductive alginate-based hydrogel bioink capable of promoting vascular network formation and tubulogenesis in a coculture of human umbilical vein endothelial cells (HUVECs) and human adipose-derived mesenchymal stem cells (hADSCs). We engineered the microenvironment of our bioink to be vasculogenic by conjugating synthetic integrin-binding peptides (RGD) and protease-sensitive VEGF receptor-binding peptides (MMPQK) to the backbone of partially oxidized alginate using orthogonal "click" chemistry. Alginate hydrogels containing both RGD and MMPQK peptides were capable of promoting robust vascular network formation and synergistically enhanced vascular morphogenesis compared to hydrogels containing either peptide by itself. Initially, the hydrogel precursor solution was not viscous enough for bioprinting due to the low concentration of alginate (2% w/v). Instead of increasing the polymer concentration, we partially crosslinked the precursor with an optimal amount of calcium chloride (15 mM). This raised the viscosity of the precursor by several orders of magnitude to a suitable range for bioprinting and the bioink behaved as a weak viscoelastic solid, preventing sedimentation of suspended cells. The bioink flowed under a low yield stress and was highly shear thinning, enabling good cell viability (>90%) after extrusion. The bioink was fully crosslinked immediately after extrusion onto a calcium-containing substrate. When applied as a vascular lattice in a Vascularized Tissue Unit construct, our bioink promoted angiogenic sprouting into avascular tissue "buds" containing dermal fibroblasts. The bioink reported here could have broad application in robotic dispensing methods for directly vascularizing bioprinted tissue constructs and its defined chemistry is favorable over other natural protein-based hydrogel bioinks.