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Directed endothelial cell morphogenesis in micropatterned gelatin methacrylate hydrogels

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ABSTRACT

Engineering of organized vasculature is a crucial step in the development of functional and clinically relevant tissue constructs. A number of previous techniques have been proposed to spatially regulate the distribution of angiogenic biomolecules and vascular cells within biomaterial matrices to promote vascularization. Most of these approaches have been limited to two-dimensional (2D) micropatterned features or have resulted in formation of random vasculature within three-dimensional (3D) microenvironments. In this study, we investigate 3D endothelial cord formation within micropatterned gelatin methacrylate (GelMA) hydrogels with varying geometrical features (50–150 μm height). We demonstrated the significant dependence of endothelial cells proliferation, alignment and cord formation on geometrical dimensions of the patterned features. The cells were able to align and organize within the micropatterned constructs and assemble to form cord structures with organized actin fibers and circular/elliptical cross-sections. The inner layer of the cord structure was filled with gel showing that the micropatterned hydrogel constructs guided the assembly of endothelial cells into cord structures. Notably, the endothelial cords were retained within the hydrogel microconstructs for all geometries after two weeks of culture; however, only the 100 μm-high constructs provided the optimal microenvironment for the formation of circular and stable cord structures. Our findings suggest that endothelial cord formation is a preceding step to tubulogenesis and the proposed system can be used to develop organized vasculature for engineered tissue constructs.

1. Introduction

Organ failure resulting from disease and trauma affects millions of Americans every year. Due to the limited availability of donors, transplantation has come to be only a partial solution. The field of tissue engineering has emerged to address this problem by generating transplantable tissues and organ substitutes [1–3]. Despite significant advances in this field, several challenges still remain towards developing fully functional engineered tissue constructs. Vascularization has been one of the major bottlenecks in tissue engineering [4–7]. In particular, most of the success in this field has come from creating thin and avascular tissues such as skin, cartilage and bladder. In contrast, larger and more complex tissues and organs require an adequate blood supply for the embedded cells within a tissue engineered construct. The critical importance of vascularization for sufficient oxygenation and nutrient delivery in complex tissues (*i.e.* heart, kidney, liver) has led researchers to develop new strategies to develop vasculature networks within engineered tissues. A number of these strategies, such as immobilization of angiogenic growth factors within a biomaterials matrix [8–11], are biomimetic attempts in which endothelial cells respond to angiogenic growth factors and ultimately migrate and assemble to form three-dimensional (3D) tubular structures. In cell-based approaches, a vascular bed is engineered throughout the construct by combining different types of vascular cells prior to implantation within a host [12–15].

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