Engineering hydrogel scaffold for rapid and functional vascularization

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Statement of Purpose: Slow vascularization of functional blood limits the transplantation of tissue constructs and the recovery of ischemic and wounded tissues. Without functional vascularization, oxygen, nutrition, and cells cannot diffuse into the constructs, and the newly formed tissues do not survive the transplantation. Despite the widespread investigation of polymer-based hydrogel scaffolds for their therapeutic applications, blood vessel ingrowth into these hydrogel scaffolds remains a challenge. To promote neovascularization or angiogenesis, we have developed tunable dextran-based hydrogels by incorporating different functional groups. We hypothesized that modifying the properties of biodegradable hydrogel scaffolds and encapsulating multiple angiogenic growth factors (GFs) would induce a rapid and functional vasculature into the scaffolds. Moreover, to test the potential of the hydrogel scaffolds as tissue engineering constructs, we further examined them in a burn wound injury model to regenerate skin structures.

Methods: Incorporation of functional groups to the dextran backbone allows us to manipulate polymer properties, while the immobilization of multiple angiogenic GFs leads to a rapid proliferation of functional vasculature into the scaffolds. In this study, a series of dextran hydrogels were made and characterized in terms of swelling ratio, biocompatibility, degradation rate, mechanical strength. To optimize the hydrogel for rapid vascular ingrowth, the hydrogel structure was remodeled by decreasing crosslinking density via reduced degree of substitution of crosslinking groups. To further investigate the effect of angiogenic GFs, multiple factors were loaded into the optimized hydrogels.

To evaluate the potential of the hydrogel as a tissue engineering scaffold, we examined it using a mouse burn wound model. The burn wound generation and surgery mimicked current clinical practice. These wounds were covered with either dextran hydrogels or Integra, and non-treatment as control followed coverage with Duoderm dressings. The wound tissue was collected and assessed histologically at predetermined times.

Results: The incorporation of different functional groups affects the physical and biological properties. The reduction in crosslinking density of the optimized hydrogels offered a wide range of improved properties; results indicated that lower crosslinking density reduces hydrogel rigidity, increases hydrogel swelling, enables high levels of VEGF release, and supports rapid hydrogel disintegration and tissue ingrowth, all pivotal for efficient angiogenesis. Our results also demonstrate a synergistic effect of angiogenic GFs; the co-administration of VEGF+Ang-1 and VEGF+IGF+SDF-1 induced more and larger blood vessels than any individual GFs, while the combination of all GFs led to a dramatic increase in the size and number of newly formed functional vessels (Figure 1). Moreover, the burn study indicates that the dextran hydrogel promotes angiogenesis and complete skin regeneration.

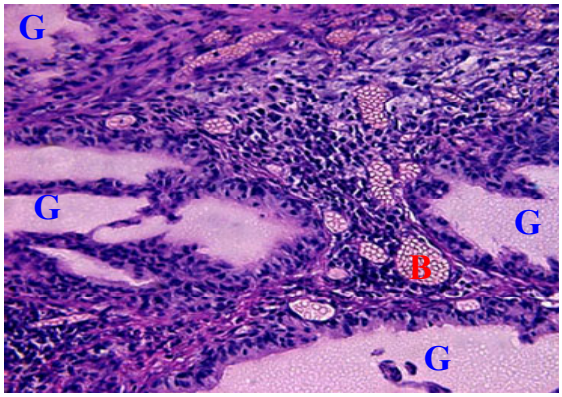

Figure 1. Functional blood vessels within the hydrogel scaffold in a subcutaneous rat model (G stands for hydrogel, B stands for functional blood vessels with red cells)

Conclusions: Dextran hydrogel scaffold can be chemically engineered in terms of chemical and physical structures, with a variety of different mechanical strength, degradation rate, swelling ratio. With precise manipulation of hydrogel scaffold properties, rapid, efficient, and functional neovascularization can be achieved. Immobilization of defined angiogenic GFs within tuned dextran hydrogels leads to abundant tissue ingrowth and functional vascularization, and is an excellent candidate for therapeutic vascularization. The wound healing study further confirmed that the hydrogel scaffolds can be tailored to enhance angiogenesis and skin regeneration.

References: 1.Sun G, Biomaterials, in press (2010) DOI,10.1016/j.biomaterials.2010.08.091.2.Sun G, J Biomed Mater Res. Part A.2010; 93A:1080-1090.