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bFGF-containing electrospun gelatin scaffolds with controlled nano-architectural features for directed angiogenesis

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ABSTRACT

Current therapeutic angiogenesis strategies are focused on the development of biologically responsive scaffolds that can deliver multiple angiogenic cytokines and/or cells in ischemic regions. Herein, we report on a novel electrospinning approach to fabricate cytokine-containing nanofibrous scaffolds with tunable architecture to promote angiogenesis. Fiber diameter and uniformity were controlled by varying the concentration of the polymeric (i.e. gelatin) solution, the feed rate, needle to collector distance, and electric field potential between the collector plate and injection needle. Scaffold fiber orientation (random vs. aligned) was achieved by alternating the polarity of two parallel electrodes placed on the collector plate thus dictating fiber deposition patterns. Basic fibroblast growth factor (bFGF) was physically immobilized within the gelatin scaffolds at variable concentrations and human umbilical vein endothelial cells (HUVEC) were seeded on the top of the scaffolds. Cell proliferation and migration was assessed as a function of growth factor loading and scaffold architecture. HUVECs successfully adhered onto gelatin B scaffolds and cell proliferation was directly proportional to the loading concentrations of the growth factor (0–100 bFGF ng/mL). Fiber orientation had a pronounced effect on cell morphology and orientation. Cells were spread along the fibers of the electrospun scaffolds with the aligned orientation and developed a spindle-like morphology parallel to the scaffold's fibers. In contrast, cells seeded onto the scaffolds with random fiber orientation, did not demonstrate any directionality and appeared to have a rounder shape. Capillary formation (i.e. sprouts length and number of sprouts per bead), assessed in a 3-D in vitro angiogenesis assay, was a function of bFGF loading concentration (0 ng, 50 ng and 100 ng per scaffold) for both types of electrospun scaffolds (i.e. with aligned or random fiber orientation).

1. Introduction

Current approaches in therapeutic angiogenesis that involve the administration of angiogenic growth factors, cells or a combination of cells and cytokines have demonstrated promising results in a number of experimental and clinical ischemic settings [1–6]. However, the long term instability and poor organization of the newly formed microvasculature that are associated with current strategies has become a major impediment towards the development of a non-invasive clinically relevant angiogenesis approach.

The extracellular matrix (ECM) is a complex structural network of proteins and carbohydrates that provides structural support to mammalian cells and regulates a number of cellular and tissue functions (i.e. cell migration and growth, wound healing) [7,8]. Structural proteins in the interstitial ECM and basement membranes contain bioactive domains that can bind to cell surface receptors, other structural proteins, or to signaling molecules such as cytokines, chemokines, and matrix proteinases [9]. A large number of bioactive molecules (i.e. growth factors) are bound via non-covalent interactions within the ECM and are released under tissue specific conditions [10]. Furthermore, specific intracellular signaling pathways can be efficiently regulated through biological cues as well as structural interactions (i.e. mechanotransduction) between ECM and the intracellular cytoskeleton [11–14]. As a result, a number of strategies in therapeutic angiogenesis have focused on integrative approaches where angiogenic growth factors and/or cells are combined with 3-D scaffolds that mimic the extracellular matrix

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