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Research Paper

Microstructure-dependent mechanical properties of electrospun core-shell scaffolds at multi-scale levels

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ABSTRACT

Mechanical factors among many physiochemical properties of scaffolds for stem cell-based tissue engineering significantly affect tissue morphogenesis by controlling stem cell behaviors including proliferation and phenotype-specific differentiation. Core-shell electrospinning provides a unique opportunity to control mechanical properties of scaffolds independent of surface chemistry, rendering a greater freedom to tailor design for specific applications. In this study, we synthesized electrospun core-shell scaffolds having different core composition and/or core-to-shell dimensional ratios. Two independent biocompatible polymer systems, polyetherketoneketone (PEKK) and gelatin as the core materials while maintaining the shell polymer with polycaprolactone (PCL), were utilized. The mechanics of such scaffolds was analyzed at the microscale and macroscales to determine the potential implications it may hold for cell-material and tissue-material interactions. The mechanical properties of individual core-shell fibers were controlled by core-shell composition and structure. The individual fiber modulus correlated with the increase in percent core size ranging from 0.55 ± 0.10 GPa to 1.74 ± 0.22 GPa and 0.48 ± 0.12 GPa to 1.53 ± 0.12 GPa for the PEKK-PCL and gelatin-PCL fibers, respectively. More importantly, it was demonstrated that mechanical properties of the scaffolds at the macroscale were dominantly determined by porosity under compression. The increase of scaffold porosity from $70.2\% \pm 1.0\%$ to $93.2\% \pm 0.5\%$ by increasing the core size in the PEKK-PCL scaffold resulted in the decrease of the compressive elastic modulus from 227.67 ± 20.39 kPa to 14.55 ± 1.43 kPa while a greater changes in the porosity of gelatin-PCL scaffold from $54.5\% \pm 4.2\%$ to $89.6\% \pm 0.4\%$ resulted in the compressive elastic modulus change from 484.01 ± 30.18 kPa to 17.57 ± 1.40 kPa. On the other hand, the biphasic behaviors under tensile mechanical loading result in a range from a minimum of 5.42 ± 1.05 MPa to a maximum of 12.00 ± 1.96 MPa for the PEKK-PCL scaffolds, and 10.19 ± 4.49 MPa to 22.60 ± 2.44 MPa for the gelatin-PCL scaffolds. These results suggest a feasible approach for precisely controlling the local and global mechanical characteristics, in addition to independent control over surface chemistry, to achieve a desired tissue morphogenesis using the core-shell electrospinning.

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1. Introduction

Tissue engineering approaches provide a viable method for the replacement or regeneration of damaged/diseased tissues. Tissue scaffolds need to be specifically designed for target tissues in order to modulate cells to elicit appropriate phenotypic behaviors and subsequent tissue morphogenesis (Fisher and Mauck, 2013; Langer and Vacanti, 1993). When designing and engineering such tissue replacements, it is critical to address various requirements to meet the biochemical and physical traits of the native tissues. Thus, an in-depth understanding of the interaction between the cells and the physiochemical properties of the scaffolds is essential for enhancing efficacy of the implanted tissue for successful therapeutic tissue regeneration (Khademhosseini et al., 2006; Leach, 2006; Stevens and George, 2005; Xu and Simon, 2005). This fundamental understanding is especially important when stem cells are considered as a cell source for the regeneration of tissues. The behaviors (i.e., proliferation and differentiation) of stem cells such as induced pluripotent stem cells (iPSC), adipose-derived stem cells (ASC), and mesenchymal stem cells (MSC), have shown to be controlled by their microenvironments or ‘cell niche’ (Engler et al., 2006; Park et al., 2011; Pek et al., 2010). In addition to soluble factors, physical environmental factors significantly affect stem cell behaviors. Specifically, mechanical properties of scaffolds (e.g., stiffness) have shown to direct stem cell differentiation independent from material surface chemistry (Huang et al., 2005; Nam et al., 2011). In addition, mechanically different scaffolds elicit different compliances to extrinsic mechanical forces in dynamic culture environments, which subject residing cells to different stress/strain environments to modulate stem cell behavior (Nerurkar et al., 2011). Therefore, scaffolds with well-designed and precisely controlled mechanical properties are essential to enhance tissue morphogenesis of stem cell-based engineered tissue.

The mechanical characteristics of the scaffold influence the differentiation of progenitor cells towards desired phenotypic tissue possibly via modulating the attachment and spreading of the cells that regulate cell morphology. Several studies have shown that control of stem cell morphology via substrate stiffness determines subsequent stem cell differentiation, suggesting the mechanical properties as an important design criterion for scaffolds (Binulal et al., 2010; Engler et al., 2006; Maldonado et al., 2015; Park et al., 2011; Pek et al., 2010). In addition to the ‘intrinsic’ mechanical properties of scaffolds, their performance under extrinsic mechanical stimuli, i.e., forces generated by bodily movement *in vivo* or ‘mechanical training’ of engineered tissues *in vitro*, is just as influential for directing stem cell differentiation. For example, dynamic compressive or tensile loading to stem cell/scaffold constructs that mimics the native mechanical environments has shown to induce phenotype-specific differentiation of stem cells, e.g. compressive and tensile forces for chondrogenesis and tendonogenesis, respectively (Bosworth et al., 2014; Lee et al., 2010; Mauck et al., 2000; Moroni et al., 2006). Such *in-vivo*-like extrinsic mechanical stimulation to the cells within scaffolds is likely determined by the bulk or macroscale mechanical properties of the scaffolds. Not only the

mechanical loading direct stem cell differentiation, but it is also essential for maintaining tissue-specific phenotypes of the differentiated cells to support tissue maturation (Bosworth et al., 2014; Gurjarpadhye et al., 2015; Seliktar et al., 2000). Therefore, tissue engineers must simultaneously take into account the macroscale mechanical characteristics of scaffolds for controlled tissue morphogenesis as well as the microscale level properties that control cellular behaviors through modulating the localized cell-material interactions.

With this in mind, electrospinning presents a cost-effective and versatile technique for fabricating nano-/micro-structures possessing a high surface area-to-volume ratio, suitable for tissue engineering scaffolds. It also provides precise control over the physical and biological properties via control over various electrospinning parameters including solution properties (natural or synthetic polymer/solvent concentration, viscosity, conductivity) and processing parameters (solution flow rate, applied electric field, collection distance) (Li et al., 2002). The fibrous scaffolds that resemble the morphology of native extracellular matrix (ECM) have shown to be capable of addressing a vast array of potential bioengineering applications (Blackstone et al., 2014; Bosworth et al., 2014; Moroni et al., 2006; Nerurkar et al., 2011; Schenke-Layland et al., 2009). Recently, we have shown that the stiffness of electrospun scaffolds modulates self-renewal of iPSCs (Maldonado et al., 2015) and differentiation of MSCs (Nam et al., 2011). In addition, we have also shown that electrospun scaffolds provide an appropriate platform to actuate scaffold-seeded cells with physiological mechanical stimulation, resulting in enhanced tissue morphogenesis (Nam et al., 2009).

In this regard, core-shell (also referred to as coaxial or core-sheath) electrospinning further allows for tight control over the physiochemical properties of the scaffolds. The method utilizes concentric needles to encapsulate one material within another in the form of monolithic fibrous structure. Advantages of the core-shell structure include the capability of embedding growth factors or drugs (Jiang et al., 2005; Jiang et al., 2006), or more relevantly in this study, the modulation of the intrinsic mechanical properties while maintaining the homogenous surface chemistry of the shell (Blackstone et al., 2014; Sun et al., 2003). Utilizing an identical shell material with varied core size/material composition enables decoupling of the mechanical factors from the surface chemistry of the scaffolds. This maintains a chemically uniform exterior for cell interaction while providing a means to subject the cells to independently controlled mechanical environments (Zhang et al., 2004, 2005). More importantly, individual electrospun fiber mechanics can be controlled independently from the macroscale scaffold mechanics, presenting further engineering control over the physiochemical properties for various *in vitro* and *in vivo* applications.

The objective of this study is to understand the relationship between the microscale (i.e. individual fibers) and macroscale (i.e. bulk fibrous scaffolds) mechanical properties of electrospun core-shell scaffolds. The influence of polymer materials and dimensions of the core-shell structures on the mechanical characteristics of these scaffolds were evaluated. Ultimately, we demonstrate a methodology to control the intrinsic individual fiber mechanics independent of the bulk

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