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Enhancing cell infiltration of electrospun fibrous scaffolds in tissue regeneration

Jinglei Wu [a, b], Yi Hong [a, b, *]

[a] Department of Bioengineering, University of Texas at Arlington, Arlington, TX 76019, USA
[b] Joint Graduate Program in Biomedical Engineering, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

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ABSTRACT

Electrospinning is one of the most effective approaches to fabricate tissue-engineered scaffolds composed of nano-to sub-microscale fibers that simulate a native extracellular matrix. However, one major concern about electrospun scaffolds for tissue repair and regeneration is that their small pores defined by densely compacted fibers markedly hinder cell infiltration and tissue ingrowth. To address this problem, researchers have developed and investigated various methods of manipulating scaffold structures to increase pore size or loosen the scaffold. These methods involve the use of physical treatments, such as salt leaching, gas foaming and custom-made collectors, and combined techniques to obtain electrospun scaffolds with loose fibrous structures and large pores. This article provides a summary of these motivating electrospinning techniques to enhance cell infiltration of electrospun scaffolds, which may inspire new electrospinning techniques and their new biomedical applications.
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1. Introduction

First demonstrated in the 1930s by Anton Formhals, electrospinning has increasingly gained attention for various applications in the research community and industrial field [1]. Featured characteristics including simplicity and affordable cost, as well as

* Corresponding author. Department of Bioengineering, University of Texas at Arlington, Arlington, TX 76019, USA.
E-mail address: yihong@uta.edu (Y. Hong).
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controllable fiber diameter and arrangement of electrospinning technique make it a versatile approach to fabricating scaffolds with variable properties. One prominent feature of electrospun scaffolds is its ultrafine fibrous structure that reassembles the nanoscale of native extracellular matrix (ECM). They possess a large surface-to-volume ratio and are extremely conducive for cell attachment and growth. Therefore, they are widely used for tissue replacement and regeneration, including the myocardium [2], blood vessel [3,4], heart valve [5], skin [6], bone [7,8], cartilage [9], tendon [10], meniscus [11] and nerve [12].

Electrospun scaffolds made from synthetic, natural, or combined materials have a nanofibrous structure that bears a close resemblance to native ECM. This structure provides the scaffolds with essential cues for cell growth and organization. Cell proliferation and ECM deposition on the electrospun scaffold have been well elaborated upon [13]. The conventional nanofibrous scaffolds (Fig. 1) merely mimic native ECMs in their fibrillary structures but not in their spatial characteristics. Specifically, during a conventional electrospinning process, generated fibers are densely compacted on a solid plate. The resulting electrospun scaffold is a planar substrate with a small interfiber distance much less than cell size. When cultured on conventional electrospun scaffolds, the cells experience a two-dimensional growth pattern with minimal penetration (Fig. 2) rather than a three-dimensional organization of cells embedded in native ECMs. Such poor cell infiltration into the scaffold due to the dense fibrous structure poses a significant challenge for tissue regeneration. Cell infiltration is essential for the formation of a three-dimensional (3D) cell-scaffold construct, subsequently promoting tissue ingrowth and facilitating integration between scaffold and host tissue post-implantation. Consequently, many significant techniques have been developed to improve cell infiltration for electrospun scaffolds [14,15]. In this article, we review recent progress in promoting cell infiltration into the electrospun scaffolds by altering scaffold structure via a variety of techniques (Table 1).

2. Techniques to enhance cell infiltration of electrospun scaffolds

2.1. Combination of nano and micro-fibers

Combining large microfibers with fine nanofibrous scaffolds can produce large pores with great pore interconnectivity. Balguid et al. illustrated that pore size strongly depended on fiber diameter, which ultimately determined the cell penetration behaviors of electrospun scaffolds [16]. The nanofibers exhibit advantages in improved cell adhesion and proliferation, while microfibers are advantageous in making pore size bigger and promoting cell infiltration [17,18]. This leads to the methodology of combining nanofibers and microfibers to fabricate a scaffold that uses the inherent advantages of both electrospun fibers (Fig. 3A).

Electrospun nano-/micro-fiber hybrid scaffolds can be prepared by two-stream electrospinning, where one stream creates nanofibers and the other generates microfibers. Pham et al. reported a poly(ε-caprolactone) (PCL) scaffold composed of 5 μm microfibers interspersed with 600 nm nanofibers supported completed cell infiltration throughout the whole scaffold in a bioreactor within 12 days [19]. Large pores defined by the microfibers allowed cells to infiltrate the scaffold freely, while the nanofibers facilitated cell spreading and improved cell growth inside the scaffold [20]. Furthermore, the presence of nanofibers in the nano-/micro-fiber hybrid scaffolds influenced stem cell differentiation [20,21]. Levorson et al. demonstrated that fibrin nanofibers interspersed in a nano-/micro-fiber scaffold have a positive effect on the chondrogenic differentiation of human mesenchymal stem cells (MSCs) as increased glycosaminoglycan (GAG) production was found in two weeks of culture without the addition of growth factors [21].

2.2. Electrospinning with salt leaching

Salt leaching has been extensively used to prepare 3D porous scaffolds for tissue engineering applications. Salt particles are dispersed evenly in a polymer solution and leached out to create large pores with controllable pore size determined by particle size. Based on this principle, combining electrospinning with salt leaching leads to fibrous scaffolds with large pores. Nam et al. reported that the introduction of tiny salts (90–106 μm in diameter) into the Taylor Cone using a sheath surrounding the needle at intervals during electrospinning of PCL produced a uniform fiber network with a well-spread distribution of salt particles (Fig. 3B) [22]. Subsequently, salt leaching results in improved porosity and large pores with increased delamination within the PCL fibrous scaffold. After 3 weeks of culture, CFK2 cells (a cell line derived from fetal rat calvariae that has the phenotypic characteristics of chondrocytes) exhibited an extensive infiltrated depth of 4 mm along with up to 70% cell coverage within the delaminated scaffolds. Unlike adding salt particles into the Taylor Cone during the intervals of electrospinning, Kim et al. produced a homogeneous porous hyaluronic acid/collagen porous mesh by simultaneously depositing salt particles with nanofibers during electrospinning [23]. The resultant porous scaffold maintained structural integrity with acceptable dimensional shrinking after salt leaching. Bovine chondrocytes exhibited the roundness characteristic of typical chondrocyte phenotypes with extracellular matrix accumulation inside the scaffolds.

2.3. Cryogenic electrospinning

Using ice crystals as a porogen to induce large pores inside electrospun scaffolds was first published by Simonet et al. [24] and is also termed cryogenic electrospinning by Leong et al. [25,26]. This approach involves the use of a low-temperature collecting system that allows the simultaneous formation of nanofibers and ice crystals, yielding an ice particle-embedded fibrous mesh (Fig. 3C). The ice particles are subsequently removed by freeze-drying to create pores inside the electrospun scaffolds. Therefore, the porosity and pore size of scaffolds are adjusted by varying the size and amount of the embedded ice crystals. Scaffold porosity increases with a greater amount of embedded ice crystals [24], and by alternating the humidity of the electrospinning environment to vary the size of ice crystals, the scaffold pore size can be adjusted from 10 to 500 μm [25]. The NIH 3T3 fibroblasts penetrated a 50 μm-thick porous scaffold under static culture condition within 7 days and showed a continuously increased number of cells during a period of 14 days, whereas no cell infiltration was found in conventional electrospun scaffolds. The ice crystal induced scaffold (400 μm thick) was then subcutaneously implanted into rat dorsum. Similar to the *in vitro* study, improved cell infiltration with macrophages and collagen-producing fibroblasts throughout the ice crystal induced scaffold at day 56, while poor cell infiltration was seen in the conventional electrospun scaffold [25]. Cryogenic electrospinning was also used for the chemoresistance of cancer cells by Bulysheva et al., where cryogenic electrospun silk fibroin (SF) scaffolds were fabricated to mimic cancer ECM [27]. HN12 cells derived from human head and neck squamous cell carcinoma were seeded with cryogenic electrospun SF scaffolds and then compared with an *in vivo* model of the same derivative human cancer to investigate cell-matrix interactions and drug resistance. Due to its highly porous structure, the cryogenic electrospun scaffold

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