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Fabrication of novel high surface area mushroom gilled fibers and their effects on human adipose derived stem cells under pulsatile fluid flow for tissue engineering applications

Stephen A. Tuin [a], Behnam Pourdeyhimi [b], Elizabeth G. Loboa [a,c,*]

[a] Joint Department of Biomedical Engineering at North Carolina State University and the University of North Carolina at Chapel Hill, 4208 EB3, Campus Box 7115, Raleigh, NC 27695-7115, USA
[b] The Nonwovens Institute at North Carolina State University, College of Textiles, 2401 Research Drive, Raleigh, NC 27695, USA
[c] Department of Materials Science and Engineering at North Carolina State University, EB 1, Room 3002, Raleigh, NC 27695, USA

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ABSTRACT

The fabrication and characterization of novel high surface area hollow gilled fiber tissue engineering scaffolds via industrially relevant, scalable, repeatable, high speed, and economical nonwoven carding technology is described. Scaffolds were validated as tissue engineering scaffolds using human adipose derived stem cells (hASC) exposed to pulsatile fluid flow (PFF). The effects of fiber morphology on the proliferation and viability of hASC, as well as effects of varied magnitudes of shear stress applied via PFF on the expression of the early osteogenic gene marker runt related transcription factor 2 (RUNX2) were evaluated. Gilled fiber scaffolds led to a significant increase in proliferation of hASC after seven days in static culture, and exhibited fewer dead cells compared to pure PLA round fiber controls. Further, hASC-seeded scaffolds exposed to 3 and 6 dyn/cm^2 resulted in significantly increased mRNA expression of RUNX2 after one hour of PFF in the absence of soluble osteogenic induction factors. This is the first study to describe a method for the fabrication of high surface area gilled fibers and scaffolds. The scalable manufacturing process and potential fabrication across multiple nonwoven and woven platforms makes them promising candidates for a variety of applications that require high surface area fibrous materials.

Statement of Significance

We report here for the first time the successful fabrication of novel high surface area gilled fiber scaffolds for tissue engineering applications. Gilled fibers led to a significant increase in proliferation of human adipose derived stem cells after one week in culture, and a greater number of viable cells compared to round fiber controls. Further, in the absence of osteogenic induction factors, gilled fibers led to significantly increased mRNA expression of an early marker for osteogenesis after exposure to pulsatile fluid flow. This is the first study to describe gilled fiber fabrication and their potential for tissue engineering applications. The repeatable, industrially scalable, and versatile fabrication process makes them promising candidates for a variety of scaffold-based tissue engineering applications.

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1. Introduction

In this manuscript, we describe for the first time the fabrication of a novel fiber cross sectional morphology, which we have termed "gilled" fibers, for their resemblance to the underside of a mushroom cap. Gilled fibers consist of an outer solid poly(lactic acid) (PLA) shell, with multiple finger like PLA projections extending toward an internal hollow channel. Gilled fiber processing to fabricate carded nonwoven fabrics as scaffolds for tissue engineering applications is evaluated and discussed.

Tissue engineering strategies for the creation of new functional bone tissue using a stem cell source require recapitulation of the chemical and mechanical environment of the native tissue being replaced. It is well known that chemical cues are capable of regulating differentiation of a variety of stem cell sources. However, in

* Corresponding author at: College of Engineering, Office of the Dean, W1051 Thomas & Nell Lafferre Hall, Columbia, MO 65211, USA.
E-mail addresses: satuin@ncsu.edu (S.A. Tuin), bpourdey@ncsu.edu (B. Pourdeyhimi), egloboa@missouri.edu (E.G. Loboa).

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the past few decades, we and others have shown the critical role of the mechanical environment in controlling stem cell fate [1–4], including tensile strain [5–10], shear stress [11–13], and hydrostatic pressure [14,15]. In the context of bone tissue engineering, compressive forces exerted on bones during normal day-to-day movement result in pressure driven flow of interstitial fluid through canaliculi, exposing mechanosensitive osteocytes to shear stress [12,13,11,16,17]. Osteocytes have been shown to respond to these changes in shear stress and initiate an appropriate cellular response [12,11,16]. Bone tissue experiences shear stresses in the range of 8–30 dyn/cm^2 during normal physiological loading, with 30 dyn/cm^2 representing peak loading during extensive physical activity [18].

As a result, researchers have investigated the use of biomimetic magnitudes of shear stress for functional bone tissue engineering applications using stem cells. Multiple studies have evaluated the impact of fluid shear stress, both pulsatile and oscillatory, on osteocytes [12,13,16,17,19,20] and bone marrow derived mesenchymal stem cells (MSC) [20]. They have shown that shear stresses consistent with shear stresses that occur in bone during normal physiological loading increase osteogenesis and new bone formation [12,13,16,17,19,20]. Human adipose derived stem cells (hASC), a relatively more abundant and accessible stem cell source than MSC, have also been shown to be mechanosensitive to shear stress [1,11,21]. Human ASC are an attractive candidate for a variety of tissue engineering strategies due to their relative ease of harvest compared to MSC and other stem cell sources. Human ASC can be readily obtained from routine liposuction and abdominoplasty procedures. We and others have shown that hASC are capable of multipotent differentiation, including adipogenesis, osteogenesis, and chondrogenesis [9,14,22–30].

Shear stress has been shown to upregulate osteogenesis of ASC cultured on two dimensional substrates seeded with cells and exposed to pulsatile fluid flow (PFF) [11]. However, for the generation of three dimensional tissues, an initial biodegradable scaffolding structure is needed for early attachment of hASC, providing initial structural integrity, and capable of withstanding applied fluid flow. Our group and many others have reported on the use of PLA, an FDA-approved biodegradable polymer, for use in the creation of tissue engineering scaffolds [22,31–35]. The degradation rate of PLA can be tuned by altering the polymer properties, such as molecular weight and crystallinity, to achieve the desired rate of degradation for a particular application [36]. In this study, co-spinning of PLA using a specialized winged fiber spinnerette with AQ55S as a second, sacrificial polymer, facilitates the formation of the unique gilled fiber cross section. AQ55S is a commercially available water dispersible amorphous sulphonated copolyester (Eastman Chemical Company, Kingsport, TN). The 55 in the polymer name indicates a glass transition temperature of 55 °C. The water dispersible nature of AQ55S is attributed to sodiosulpho groups on the polymer backbone. AQ55S readily disperses in water at temperatures above 55 °C, making it an attractive sacrificial component compared to polymers that require solvent to disperse.

While many studies have reported on the successful implementation and utilization of PLA and other polymers for tissue engineering scaffolds, critical challenges remain with large scale fabrication and scale up of biomimetic scaffolds. We hypothesize that nonwoven scaffolds composed of PLA are well suited to meet this need. In general, nonwovens are an arrangement of random fibers bonded together to create a web or fabric. The fibrillar structure of nonwovens mimics that of native extracellular matrix (ECM), and provides an ideal environment for cellular attachment and proliferation [37–39]. In particular, we propose that, carded nonwoven fabrication techniques are capable of producing repeatable, scalable, high speed, and economical scaffolds from a wide variety of fiber types, including PLA. In the carding process, staple fibers (short fibers of about 5 cm in length) are first separated into individual filaments and subsequently entangled together (Fig. 1c). Fiber entanglement is achieved via a series of specialized combed rollers, and the resultant web can be layered many times to achieve a desired thickness (termed crosslapping). Finally, the structure is locked in place by bonding the fibers via a variety of methods, such as needle punching, hydroentangling, thermal bonding, or chemical adhesives [40–43].

The goal of this study was to use carding technology to fabricate nonwoven scaffolds for bone tissue engineering applications and to test these scaffolds for their ability to support hASC viability, proliferation, and osteogenic differentiation while exposed to fluid shear stresses at magnitudes consistent with those that occur *in vivo*. The high surface area and gilled structure of the fibers described here makes them an attractive candidate for nonwoven tissue engineering scaffolds seeded with stem cells and mechanically stimulated with PFF. We hypothesized that the gilled structure would lead to enhanced mass transport properties via capillary action, resulting in locally increased levels of shear stress magnitudes, and increased osteogenic differentiation of hASC seeded on the scaffolds.

2. Materials and methods

2.1. Fabrication of gilled fiber scaffolds

2.1.1. Fabrication of gilled multifilaments

PLA grade 6100D (NatureWorks LLC, Minnetonka, MN) and AQ55S (Eastman Chemical Company, Kingsport, TN) were used for creation of all fibers. Prior to filament spinning, the rheological properties of pure PLA and AQ55S were determined on a Rosand RH7 capillary rheometer (Malvern Instruments, Malvern, UK). Polymers were dried overnight under vacuum at 85 and 40 °C for PLA and AQ55S, respectively, to remove any absorbed water. Approximately 35 g were loaded into the rheometer chamber fitted with a long die (16 mm length and 1 mm diameter) and subjected to a shear rate sweep from 20 to 10,000 s^{-1} at constant temperature. PLA and AQ55S were each evaluated at 230 and 250 °C.

Gilled fiber multifilaments were fabricated using a winged fiber spinnerette (NatureWorks LLC, Minnetonka, MN). Fabrication of winged fibers, consisting of a solid fiber with multiple "winged" projections with a cross section approximating an asterisk has been previously described [44]. This is the first study to report the fabrication of gilled fibers using a winged fiber spinnerette (the hollow gilled channel is shaped like a winged fiber). In brief, PLA was loaded as the core polymer with AQ55S forming the bicomponent sheath at a 50:50 ratio by weight (w/w). Multifilaments were extruded at a throughput of 0.9 g per hole per minute (ghm) and collected on bobbins (cylinders on which filaments were wound) at a winding speed of 2100 m/min heated to 125 °C. Goulston PL-859 spin finish (Goulston Technologies INC, Monroe, NC) was applied to the spinline prior to winding to prevent fibers from adhering to each other and the guide rolls. Round fiber cross section multifilaments composed of pure PLA were extruded and collected on bobbins under similar processing conditions for the fabrication of control fibers of the same fiber diameter as experimental gilled multifilaments (Fig. 1a).

2.1.2. Fabrication of carded scaffolds

Gilled fiber and round PLA control multifilaments were unwound, crimped (heat set into a zig-zag pattern), and cut into 5 cm staple fibers for the fabrication of carded scaffolds (Fig. 1b) at the Nonwovens Institute (NWI) pilot facilities (NWI, North

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