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Textile Scaffolds: A Review of Some Significant Breakthroughs in Tissue Engineering

V. Krishna kumar[1]*, N. Gokarneshan[2] and B. Padma[2]

[1]SMK Fomra Institute of Technology, Chennai, Tamil Nadu, India

[2]Department of Costume Design and Fashion, Dr.SNSRajalakshmi College of Arts and Science, Coimbatore, Tamil Nadu, India

ABSTRACT

The article reviews some significant attempts in textile scaffolds related to developments in tissue engineering. The benefits offered by micro fibrous scaffold architectures fabricated by textile manufacturing techniques have been explored. Established and novel fiber-processing techniques can be exploited in order to generate templates matching the demands of the target cell niche. The problems related to the development of biomaterial fibers (especially from nature-derived materials) ready for textile manufacturing are addressed. Attention is also paid on how biological cues may be incorporated into micro-fibrous scaffold architectures by hybrid manufacturing approaches (e.g. nanofiber or hydrogel functionalization). Textile technologies have recently attracted great attention as potential biofabrication tools for engineering tissue constructs. Using current textile technologies, fibrous structures can be designed and engineered to attain the required properties that are demanded by different tissue engineering applications. Tissue engineering often uses synthetic scaffolds to direct cell responses during engineered tissue development. Since cells reside within specific niches of the extracellular matrix, it is important to understand how the matrix guides cell response and then incorporate this knowledge into scaffold design. The goal of this review is to review elements of cell–matrix interactions that are critical to informing and evaluating cellular response on synthetic scaffolds. Therefore, this review examines fibrous proteins of the extracellular matrix and their effects on cell behavior, followed by a discussion of the cellular responses elicited by fiber diameter, alignment, and scaffold porosity of two dimensional (2D) and three dimensional (3D) synthetic scaffolds.

***Corresponding author**

V Krishna kumar, SMK Fomra Institute of Technology, Chennai, Tamil Nadu, India, Email: principal@smkfomra.net

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Introduction

The classical tissue engineering (TE) approach (in vitro expansion of cells seeded on scaffolds and subsequent implantation) has been facing various critical obstacles concerning the translation to the bedside, namely seeding time, laborious effort and cost. Hence, in recent years in situ TE has gained increasing attention [1-8]. In this more straight-forward approach, the body's own biologic resources and reparative capability are utilized by implanting a cell-free engineered biomaterial (scaffold) into the site of injury, where host stem cells or tissue specific progenitor cells are recruited [2]. In situ TE approaches have been investigated for various possible applications such as vascular grafts, nerve and hard tissue regeneration [9-11].

Tissue engineering is a multidisciplinary enterprise that combines the principles of cellular biology, biomaterials, and engineering to address the current unmet demands for organ transplantation. Fabrication of constructs with controlled mechanical properties, microstructure, and cellular distribution plays a crucial role in the engineering of functional tissues. Scaffolds made from synthetic or natural biomaterials are commonly utilized to provide mechanical support and three dimensional (3D) environments for cellular growth and function. Traditional methods for creating scaffolds including freeze-drying, particle leaching, and solvent casting generate porous constructs with interconnected pores that are suitable for delivery of nutrients to the cells [12-15]. However, the ability of these approaches for precise control over the spatial distribution of pore size and interconnectivity, mechanical properties, and structural properties is limited.

Tissue engineering uses engineering and life science structure–function relationships to restore, preserve, or improve tissue function. Understanding the interactions between cells and their extracellular matrix (ECM) is critical for this process. The ECM provides structural support to the cells and provides cues for regulating cell differentiation, attachment and morphology, migration, and immune response. The major components include proteoglycans and fibrous proteins. Proteoglycans regulate and maintain the ECM. For example, in cartilage and tendon, decorin and biglycan regulate collagen fibrillogenesis. In tumors, syndecans influence growth and invasion, and perlecan promotes angiogenesis. While in neurons, heparan-sulfate proteoglycans enhance neurite outgrowth, but chondroitin-sulfate proteoglycans inhibit neurite outgrowth [16-19]. While proteoglycans have many vital functions, some of which remain undefined, fibrous proteins comprise the most abundant portion of the ECM. This review highlights the characteristics of fibrous ECM proteins and of fabrication methods for fibers and model systems used

in musculoskeletal tissue engineering, with comparison to other tissues and cell-based systems where gaps in the literature were identified. Finally, this review examines the relationship between the fiber parameters of tissue engineered scaffolds and the cell responses (i.e., differentiation, morphology, and migration) elicited.

Cell Free Textile Scaffolds

In recent years the general understanding of the requirements imposed on scaffolds for TE applications has changed towards templates which replicate the target cell niche in terms of their structural architecture and which are capable of adapting to a changing microenvironment, thus providing optimal conditions for tissue-ingrowth, nutrient, gas and biomolecule transport and vascularization. The scaffold architecture should be dictated by the requirements of the target cell niche. To generate scaffolds with properties tailored to the targeted application, numerous manufacturing methods have been employed. Those comprise solvent casting, gas foaming, phase separation, emulsion freeze drying, additive manufacturing (AM) techniques, electrospinning and other fiber formation techniques. The versatility of textile technology allows for the fabrication of 3D spatial structures with tunable properties in the micro- and macro range [20-41]. In the past decades, textile manufacturing techniques have been used in a wide range of engineering applications such as fiber reinforced composites, construction textiles, filtration, medical textiles etc. Fiber based techniques including electro spinning have been successfully used for the manufacturing of 3D cell laden scaffolds for classical in vitro and in vivo TE approaches, which are reviewed elsewhere. Through suitable combinations of material, fiber type and manufacturing technique, fiber-based scaffolds can be engineered to obtain properties similar to native tissue and to match critical scaffold criteria. The mechanical properties can be adjusted according to the desired properties of native tissue. Besides close structural resemblance of the scaffold to native host tissue, the success of in situ TE approaches strongly relies on the scaffolds capability to recruit host stem cells or tissue specific progenitor cells. Therefore, information-rich scaffolding systems with incorporated ‘‘cell homing’’ or ‘‘recruiting’’ factors are needed Nanofiber based scaffolds have been reviewed in detail elsewhere [42-50]. Hence, in this review nanofibers are considered in terms of a major technique for scaffold functionalization and not as structure defining component.

In this article, the benefits offered by micro-fibrous scaffold architectures fabricated by textile manufacturing techniques are discussed: How can established and novel fiber-processing techniques be exploited in order to generate templates matching the demands of the target cell niche? Which are the problems related to the development of biomaterial fibers ready for textile manufacturing? How may biological cues be incorporated into microfibrous scaffold architectures? After a critical review of exemplarily selected recent studies on cell-free fiber based scaffolds for in situ TE, including clinical trials, the findings of this article are concluded in order assess the potential and limitations of cell-free fiber based scaffolds.

Benefits of Engineered Fibrous Scaffold Architectures

Textile technology offers various manufacturing methods to fabricate scaffolds with tailored properties. For centuries, textile manufacturing techniques have been used in the traditional branches of textile industry. Detailed descriptions of the principles of knitting, weaving, braiding and non-woven fabrication as well as their respective characteristics are given elsewhere. This section describes the favors principally given by fiber and textile technology to design scaffolds with adjustable properties matching the target cell niche. At the same time, limitations and shortcomings of the current state of the art in fibrous scaffold engineering are discussed. In this review, the preconditions and possibilities of textile manufacturing methods, fiber development and functionalization for the fabrication of cell-free scaffolds for in situ TE have been summarized. Studies in this field encompass a variety of engineered scaffolds from simple grafts to complex multi-material scaffolds [51-54]. The basic benefits of fibrous scaffold architectures, namely mechanical stability, porosity and degradability, are employed in most cases.

However, fibrous engineered scaffold systems stay behind the possibilities which are principally offered by textile manufacturing techniques and their combination with other
manufacturing techniques. In order to make use of the whole range of favors, there are four main issues which need to be addressed:

1. Logical combination of manufacturing techniques and materials.
2. Biomaterial fiber development.
3. Adaption of textile manufacturing techniques to the demands of scaffolds for regenerative medicine.
4. Incorporation of biological cues (e.g. stem cell homing factors).

(1) A crucial premise for successful scaffold development is that the choice of material, manufacturing techniques and biological cues must be dictated by the targeted repair-tissue. The paradox of expert knowledge in specific techniques on the one hand and a broad overview about the huge variety of existing materials and techniques on the other hand may only be solved if intense interdisciplinary collaboration is consequently pursued. The combination of appropriate materials, manufacturing and functionalization techniques must be derived from the desired scaffold-properties.

(2) Besides the well-established synthetic polymers (e.g. PLA, PGA, PLGA, PBT), recent developments in biomaterial fiber engineering enable the exploitation of the favorable material properties from materials such as collagen, chitosan, regenerated silk or recombinant proteins in fibers suitable for their processing into stable spatial scaffolds [56-59]. However, intensified studies concerning fiber properties and the in vitro and in vivo behavior of those newly developed fibers have to be conducted in order to use them for regenerative medicine. Furthermore, regulatory restrictions regarding the use of novel fibrous materials in the human body must be taken into account.

(3) The possibilities offered by textile manufacturing techniques to create structures with adjusted mechanical and porous properties may only be exploited if the manufacturing method is chosen based on the demands of the targeted tissue. Manufacturing methods have to be adapted in order to allow the combination of the fibrous architecture with other materials (e.g. nano-fibers, hydrogels), thus creating structurally hierarchical ‘‘hybrid’’ scaffolds which match the host tissue. Also, techniques by which 3D net shaped geometries (similar to AM techniques) may be fabricated from fibers are to be further developed, thus allowing simple fabrication of custom-shaped and patient specific fibrous scaffolds.

(4) Especially for in situ TE, the incorporation and sustained release of biological cues into scaffolds is crucial for their successful application. Despite this fact, the incorporation of biological cues is not looked at in most cases when fiber-based cell-free scaffolds are used for in situ TE. A functioning fiber-based

release-system for the sustained delivery of biological cues could help in achieving an important goal in guiding host cells to form a well-integrated functional structure. Therefore, intensified research is necessary. Depending on the type of engineered tissue and the application, clinical studies showed that cell-free fibrous scaffolds may be superior to or as well as conventional ''gold standard'' treatments. Besides the obvious advantages of in situ TE (off-the-shelve scaffold availability, less cost and time consumption) it has to be considered that in terms of tissue ingrowth, tissue formation and regained functionality of regenerated tissue, cell free fibrous scaffold systems do not always yield better results as their cell-seeded counterparts. With the availability of novel biomaterial fibers with sufficient mechanical performance for textile manufacturing techniques and the appropriate addition and sustained release of cell homing factors and growth factors, in situ TE approaches using cell-free fibrous scaffolds could be elevated to various clinical applications [60-64]. To make progress towards this goal, the interdisciplinary collaboration of experts in the fields of medicine, biomaterials science and textile engineering has to be consequently pursued.

Textile Technologies and Tissue Engineering

Recently, advanced biofabrication methods such as bioprinting , stereolithography, self assembly of microgel, and biotextiles [65-76] have emerged to produce complex 3D engineered tissues from living and non-living elements with exquisite control over the resulting scaffold microarchitecture and cellular distribution.

Commercial biotextiles (e.g., TIGR® Matrix, ULTRAPRO™, and INTERGARD™) are currently used as medical implants for treating pelvic organ prolapse, hernia, and vascular diseases. Recently, textile technologies have been utilized for biofabrication of fibrous scaffolds for various tissue engineering applications [74-78]. Such technologies include weaving, knitting, braiding, embroidering, and electro spinning. The versatility of textile structures allows for tailoring their architecture by controlling the fiber size and orientation, pore size and geometry, pore interconnectivity, total porosity, and surface topography. All these properties are important for controlling the physical properties and cellular behavior of the engineered constructs. In addition, by utilization of cell-laden fibers during the assembly process, the cellular distribution can be finely controlled. In this review, we will primarily focus on the current advances in the textile-based fabrication methods for tissue engineering. Recent technological advances in the manufacturing of bio fibers as building blocks of bio textiles will be highlighted. We will then explore emerging applications of bio textiles for tissue engineering and regenerative medicine.

Textile technologies have re-emerged as promising approaches for creating complex constructs from monofilament fibers and multifilament threads for various tissue engineering applications. In this section, a summary of three textile methods that allow controlling the microstructure, mechanical properties, and cellular distribution of the tissue construct is provided. Table 2 summarizes these methods and provides highlights the advantages and drawbacks of each method. It is worth noting that nonwoven constructs that are widely used in many areas of tissue engineering are out of the scope of this review. Comprehensive reviews on the application of nonwoven constructs in tissue engineering are provided by Anwarul et al. and Pham et al. [79,80].

Knitting

Knitting is a well-established textile method for creating complex 2D and 3D structures from yarns that are interlaced in a highly ordered arrangement of connected loops. In the knitting process, yarns are drawn through a previous loop to form interconnected loops. Depending on the direction of the formed loops, the knitting process is classified into two major categories of weft and warp knitting [81]. In weft knitting, stitches from the same yarn are arranged horizontally, while in warp knitting, stitches from the same yarn are arranged vertically (Figure 4b). Knitted constructs can be characterized by their course and wale, which are the number of rows passing across the width and length of the fabric, respectively. The number of wale per unit length of the fabric is a function of the density of needles (“gauge”), yarn size and type, and the applied yarn tension.

Depending on the knitting process, types of stitches, and the yarn material, fabricated constructs possess different mechanical and physical properties. Fabrics made from tuck stitches have larger pore size and are wider, thicker, and slightly less extendable than fabrics generated from regular stitches. Float stitches on the other hand provide directionality to the structure of the knitted fabrics. The warp-knitted structures show more flexibility and extendibility compared to the weft-knitted constructs. However, the weft knitting offers superior control over the pore size, porosity, and fiber alignment in the construct [82,83]. Currently, there are automated and programmable machines that are capable of creating complex 2D and 3D fabrics in large scale. For example, “Tricot” and “Raschel” machines perform warp knitting while “flatbed” and “circular” machines perform weft knitting.

Knitted scaffolds have been extensively used to engineer or to repair damaged tissues and organs. Mechanical properties and microstructure of the knitted structure are the two important parameters affecting the scaffold functionality. The pore size of the knitted fabric should be large enough (~100μm) to allow cellular ingrowth while maintaining the mechanical strength of the construct under the applied stresses. Knitted fabrics have also been employed as a reinforcing skeleton to provide structural support for a collagen or silk sponge with proper biological environment for tissue growth (Figure 4c–e). For example, knitted silk-collagen sponge scaffold has been seeded with human embryonic stem cells (hESC) and human mesenchymal stem cells (hMSCs) for tendon and ligament regeneration, respectively. In another study, scaffolds knitted from hydroxyapatite-coated silk yarns have shown enhanced osteoinductivity and osteoconductivity. Although knitted constructs have been mostly used as a reinforcing structure, there are also reports of their use as a selectively removable template for creating autologous ECM scaffolds [84-89]. The process includes culturing cells on a knitted construct with desired microstructure and removing the knitted template after the ECM deposition of the cells. With the recent advances in the development of novel biomaterials, yarns can be made with controlled degradation profiles and mechanical properties.

Knitting process involves more fibers than most biotextiles, which enables higher complexity and performance capabilities in the construct. The ability of the knitted construct to stretch makes knitted fabrics a great candidate for engineering of load-bearing tissues. With the advent of new knitting machines equipped with computer aided design (CAD) systems, 3D structures with exquisite control on their microstructure can be fabricated. Nonetheless, creating constructs with adjustable properties in different directions is still difficult with knitting.

Weaving

Weaving is one of the most ancient technologies developed by man for creating cloth [90]. In this textile method, the fabric

is formed from two distinct sets of yarns, which are interlaced normally [91, 87]. The lengthwise yarns are called warps and the weft (filling) passes through them in the lateral direction. The most common weaves include plain, satin, and twill (Figure 5a). In plain weave, each weft passes over one warp and then under the following warp and this trend will be reversed in the following row. In satin weave, warps are floating on top of a number of wefts and are more exposed in comparison to plain weave. In twill weave, on the other hand, the wefts are passed through the warps in a way that they are exposed in a diagonal fashion. Different weaves can change the flexibility and smoothness of the fabric. Another important factor that affects the looseness as well as the porosity of the generated fabric is the number of warps and wefts per square inch [92].

Weaving looms are simple and easy to use and are compatible with a wide range of materials. Consequently, the application of woven constructs has extended to multiple engineering applications including composite fabrication, fuel cell technology, and biomedical engineering. Woven structures are more flexible than knitted constructs but can endure less force in the in-plane direction. Moreover, woven fabrics are less porous than knitted structures and possess smaller pores. The in-plane mechanical properties can be improved by interlocking multiple layers of woven fabrics for the applications that require load-bearing characteristics [94]. Moreover, the use of multiple layers allows for the fabrication of thick 3D structures.

Woven fabrics have been utilized as tissue engineering scaffolds or reinforcement mats in hydrogels to tune the mechanical properties of the construct. In a pioneering study, Moutos et al. developed a microweaving loom to assemble PGA yarns into fabrics [93]. They also interlocked several layers to create a load-bearing 3D structure. The reinforcement mat was embedded within chondrocyte-laden agarose gels for cartilage tissue engineering (Figure 5b). This work was later adopted by a number of groups which fabricated reinforcing structures from silk, poly(caprolactone) (PCL), and polypropylene [95, 10]. These studies have been mostly focused on mimicking the biomechanical properties of native tissues through the utilization of woven fabrics. Recently, researchers have tried to use weaving looms for controlling cellular pattern within a construct. For example, Onoe et al. devised a micro weaving machine and assembled cell-laden hydrogel fibers to create complex constructs with controlled cell distribution [100, 15]. In another study, wet spun cell- and bead-laden hydrogel fibers were created and then assembled using a custom-built weaving loom [101, 46].

Hydrogel fibers are usually not mechanically strong, thus, the mechanical properties of the fabricated fabric will not be suitable for applications that require load-bearing characteristics. Our group has introduced the concept of composite living fibers (CLFs) with a load-bearing core and cell-laden hydrogel shell [103]. We assembled these CLFs using a weaving loom to create cell-laden fabrics. Weaving CLFs with mechanically strong core enabled us to control both cellular distribution and mechanical properties. Weaving allows fabrication of 3D constructs with tunable anisotropic mechanical properties that mimic the properties of several native tissues such as cardiac and cartilage. Weaving looms are easier to design in comparison to knitting systems for creating cell-laden structures with controlled mechanical characteristics and cell distribution. In addition, the weaving process is less mechanically harsh compared to other textile processes.

Braiding

A braided structure is comprised of three or more strands intertwined in overlapping patterns. A wide variety of 3D geometrical shapes with fine-tuned stable properties can be obtained through varying the arrangements of diagonally intertwined strands. Complex structures fabricated through braiding are differentiated from knitted or woven counterparts by the versatility they offer in axial and radial load-bearing properties, enhanced physical stability, damage tolerance and fatigue resistance in bending, torsion and traction, as well as improved abrasion resistance. A wide range of the medical textiles are manufactured using braiding technology including sutures, stents, nerve regeneration conduits, braided composite bone plates, scaffolds for ligaments tendons, and artificial cartilages [104, 105, 51, 97].

The high tensile strength and mechanical flexibility of braided structures have made them an excellent candidate for engineering of articular and connective tissues such as cartilage, tendon, and ligament. Anterior cruciate ligament (ACL) is the most commonly injured intra-articular ligament of the knee. Braiding technique has been used to develop numerous ACL grafts with biomimetic characteristics [106-110]. It has been shown that the fiber materials, morphology of the scaffold, and the interactions between the fibers play critical roles in the proper function of the engineered grafts [111,112]. A major challenge in ACL tissue engineering is regenerating articular cartilage with anisotropic and heterogeneous mechanical properties. Varying braiding angle, fiber density and number of layers, enable developing anisotropic mechanical and physical properties with adjustable gradient along any desired direction. By changing the porosity of the engineered graft from the two ends toward the middle region, cellular ingrowth can be enhanced while the mechanical properties of the engineered tissue are maintained. Utilizing numerical tools, optimized fiber configurations that provide the biomechanical requirements needed to restore the knee function were determined.

Selection of proper fiber material is another important parameter that has to be considered in the fabrication of braided tissue constructs. Synthetic materials such as poly(lactic acid-co-ε-caprolactone (PLCL) and poly(L-lactic acid) (PLLA) or composite fibers made from synthetic and natural materials such as 50% type I collagen and 50% PVA have been used for ACL tissue engineering. Synthetic materials provide the mechanical strength while the natural materials provide a more nurturing environment for the cells to grow and function.

Another well-recognized approach to enhance and direct cellular activities is to create nano features on the constructs. Electro spinning is a powerful tool for creating fibers with nanometer sizes. Yarns made from a bundle of aligned fibers can be created using electrospinning and can be intertwined to form braided scaffolds. It has been shown that the mechanical properties of such constructs mimic the mechanical behavior of native tissue and also can enhance the cellular activity when seeded with hMSCs. Moreover, such scaffolds have been modified with antibacterial biomaterials such as chitosan and used as suturing thread that were bacterial resistance [113-116].

Due to their flexibility and ability to maintain dimensional stability as well as improved radial compressive strength, braided constructs are ideal scaffolds for engineering nerve conduits. A biodegradable multilayer braided PLA fiber-reinforced conduit has been fabricated to treat a 10mm nerve gap in the rat sciatic nerve [117,118]. The results indicated that after 8 weeks implantation the scaffold was well integrated and encapsulated by the surrounding

tissue. Recently, a novel tabular PLGA construct, consisting of dense outer tube and porous inner tube, has been developed to guide and support peripheral nerve regeneration. Higher braiding density was used for the outside tube in order to serve as support for the space of the nerve regeneration and provide the required compression performance while the interior scaffold had lower PLGA fiber density to function as the matrix bridge in the nerve regeneration process.

Overall, braided constructs offer enhanced mechanical properties under various loading conditions, good flexibility and structural stability, as well as controlled tissue regeneration. These parameters make them an apt choice for tissue reinforcement, grafts in load-bearing. fixations and wound closure and support. However, a key challenge associated with braided tissue scaffolds is their low porosity, which can limit cellular penetration and proliferation. Nevertheless, strategies that allow for the incorporation of cells into the fibers prior to their assembly can overcome this challenge.

Emerging Applications of Biotextiles

With the advent of textile technologies as bio fabrication methods for creating bio fabrics and tissue constructs, different applications of such structures have been emerged. The fabrics made from advanced biomaterials have been mainly used for three major applications including cardiovascular and musculoskeletal tissue engineering, wound dressings, and wearable electronics. However, few recent studies have reported the use of textile methods for neural tissue engineering, engineering of bladder, and for drug delivery applications.

Cardiovascular tissue engineering

Musculoskeletal engineering

Wound dressing

Wearable electronics

Challenges and Future Prospects

Biotextiles hold a great promise for applications in tissue engineering and regenerative medicine. The versatility of textile techniques provides exciting opportunities in engineering scaffolds and tissue-like structures with controlled microarchitecture and cellular distribution. Textiles are highly porous and permeable to nutrients, oxygen, and growth factors. Textile tissue engineering allows simultaneous control of mechanical properties and cell distribution within a construct. Thanks to their one directional features, fibers can provide directionality to the cells which can lead to improved cellular alignment, and controlled differentiation during the tissue formation and remodeling. Additionally, fibers can carry cells, drugs, and growth factors into the construct. Moreover, sacrificial fibers can be interwoven to facilitate the generation of pre-vascularized tissue constructs.

Despite numerous advantages offered by textile technology, there are still several challenges that have to be addressed to use this technology up to its full potential. The main obstacle for the use of bio textiles for tissue engineering and regenerative medicine is combining state-of-the-art textile machinery, novel biomaterials, and biological advances to create tissues and organs automatically. Although fibers made from synthetic materials are mechanically strong and can be assembled into complex structures using textile approaches, the harsh manufacturing process hampers the ability to encapsulate cells inside them. Current methods for creating cell-laden fibers yield to the fabrication of fibers that are not mechanically strong to withstand the mechanical loads exerted during the manufacturing process. Such challenge has been recently addressed by developing composite living fibers (CLFs) that were composed of a mechanically strong core material coated with a cell-laden hydrogel layer [119]. However, the surface of CLFs is also slippery which can make their assembly challenging. Thus, more advanced fiber fabrication techniques should be developed to allow the fabrication of cell-laden fibers with properties comparable to the currently used threads. Accordingly, it is expected that the field of textile tissue engineering will significantly move towards this direction. To allow assembly of cell-laden fibers, new textile machines that can control humidity, oxygen, and CO2 level, create a sterile environment, and facilitate nutrient access to cells within the fibers and generated fabrics is required.

While great advancements have been made in the field of biotextiles, implantable fabrics are in use for limited applications. The main challenge is the inability to capture the in vivo mechano-biological properties of different organs and tissues. This challenge can be addressed by creating different fibers from advanced biomaterials with tunable physico-chemical properties capable of delivering growth factors and chemokines. Another potential direction for the use of textile-based tissues is creating in vitro disease models and drug testing platforms. By assembly of cell-laden fibers, different cells can be interfaced to facilitate the cross-talk between multiple cell types within a tissue. These advanced living fabrics can be combined with current organ-on-a-chip platforms. Flexible and wearable electronics and sensors are other areas that have been benefitted from advances in biotextile engineering. It is expected that the field will grow towards engineering implantable and biodegradable sensors and devices fabricated from textiles. One area that can likewise see a noticeable attention is the incorporation of electronics within tissue scaffolds for monitoring cellular activity or stimulating them.

Synthetic Scaffolds – Cellular Response to Fibre Parameters

Tissue engineered scaffolds provide a structural framework that resembles the fibrous protein component of the ECM. There are several approaches to scaffold fabrication: natural polymers produced by cells, synthetic polymers, or a combination thereof. Natural polymers provide relevant biomimetic properties and cell signaling cues but offer little control over the scaffold structural or architectural properties, i.e., fiber diameter, alignment, or porosity. Conversely, synthetic polymers provide improved control over the scaffold structure and micro-architecture, but few matrikines or other biomimetic cues, without additional process engineering. Finally, both three-dimensional (3D) scaffold systems and more simple one (1D) and two (2D) dimensional models can examine mechanisms of cell interactions with fibers to inform larger scale fabrication methods. Lithography involves printing a pattern into a flat synthetic polymer surface using one of several variations to the basic method. Lithography methods offer consistent, easy to produce 1D and 2D systems, with highly controllable fiber parameters. However, changing the pattern master is nontrivial and time consuming.

Microphoto patterning produces 1D and 2D fiber systems using a multiphoton microscope. Using computer-software generated patterns makes it easy to alter the master pattern. The fiber parameters are limited by the microscope's resolution. Microphoto patterning provides a simple method to study cellular mechanisms of migration and matrix production and the use of glass-coverslip bottomed dishes facilitates various imaging, histological or immunostaining techniques. Electrospinning produces 3D scaffolds by using an electric field. Randomly oriented fiber scaffolds are collected on a grounded solid or liquid media . Aligned fiber scaffolds are formed in a variety of ways: using a rotating disc or mandrel, patterned electrodes, air-gap techniques, a patterned insulator, or high strength ceramic or electromagnets with copper plates. Electro spinning is used to

produce prototypical biomaterial scaffolds for tissue engineering for tendon,bone, cartilage, meniscus, smooth and skeletal muscle, and neural tissue and produces highly tunable scaffold structure and architecture. Electrospinning parameters such as voltage, flow rate, distance to the collector, polymer concentration, solution conductivity, solvent, humidity, and temperature determine the fiber characteristics. Fibers parameters can be finely tuned. The addition of a second electrode and a 2D moving platform allows for focused fiber control and custom-defined, open-pore scaffold architectures, which is a promising technique for creating tissue microenvironments [120-140]. Electrospun scaffolds are also fabricated using recombinant protein-based polymers, such as elastin-like recombinamers, which are biocompatible and allow for incorporating protein functional domains (e.g., argininеglycine-aspartic acid RGD) peptide motif) into the fibers . However, while electrospinning offers substantial control over the scaffold parameters, it produces small volumes of scaffold at low rates. Furthermore, electro spinning requires the use of solvents, which can be toxic. Nonetheless, electro spinning is a versatile method to produce fibers for tissue engineering, as reviewed recently. Melt electrospinning is similar to electrospinning, but the polymer is melted rather than in solution. However, after the melted polymer enters the electric field, due to the melt's high viscosity and the proximity to the collector, the polymer jet moves to the collector in a more controlled manner than in electrospinning as it cools and crystallizes. Therefore, melt electro spinning creates highly structured scaffolds. Furthermore, adding moving collectors defines a technique known as melt electro spinning writing (MEW), a form of 3D printing. Melt electro spinning offers the advantages of predictable scaffold structure and architecture, along with the use of no solvents. As for electro spinning, in melt electro spinning, the flow rate, the extrusion needle diameter, and molecular weight control fiber diameter, but in MEW, the pressure in the air gap and the collector speed collector provides additional control. In all forms of electrospinning, distance to the collector and voltage at the extrusion needle or nozzle influence fiber properties, but the effect of voltage on the fiber properties is debatable for melt electrospinning. Melt electro spinning and MEW have been used to produce scaffolds for bone, cartilage, cardiovascular, dermal, and neural tissue engineering.

Wet spinning is one of the oldest methods of producing fibers from polymers but is less commonly used for tissue engineering. In wet spinning, the polymer is dissolved using a non-volatile solvent. The solvent is then drawn out by a chemical reaction or washed out through spinnerets into a bath. The solvent is then removed in a liquid coagulation medium, leaving the polymer, which forms fibers. Wet spinning has mostly been used as a scaffold for bone tissue engineering, but it has also been used for soft tissue, vascular, dermal, and neural tissue engineering, as well as for wound dressings and drug delivery [141-156]. While wet spinning is a more rapid fabrication process (7–150 m/min) than electro spinning, it requires multiple wash steps to remove processing impurities.

Melt blowing has recently been re-purposed to produce synthetic polymer scaffolds in tissue engineering. First patented in the 1930s, melt blowing is used to produce materials like surgical drapes, hygiene products, and filtration devices. In recent work, melt blowing has been used in neural, vascular, bone, adipose, and tendon tissue engineering. Melt blowing has a major advantage over electro spinning as it can produce fabrics at rates up to 5000 m/min and requires no harsh solvents. Fabrics produced by melt blowing have fibers diameters from 500 nm to hundreds of microns in diameter, exhibit alignment and anisotropy, and range in porosity from 70 to 99% [158-164]. Melt blowing is a promising method for studying cellular mechanisms and tissue response, with proven high-throughput scalability for translation.

Dynamic Scaffolds

Recent studies have investigated cell behavior in response to dynamic scaffolds that mimic the ever-changing, in vivo environment. Dynamic scaffolds using shape-memory polymers change fiber diameter, alignment, and porosity of a scaffold reversibly via temperature change or magnetic fields [165-168]. As environments changed from randomly oriented fibers (or channels) to aligned fibers, cells aligned with the fibers; the cell morphology changed from a rounder shape on the random fibers to an elongated spindle shape in the aligned environment. The area and shape of A7R5 rat smooth muscle cells changed with acute changes in topography roughness, but morphology remained constant over extended periods of oscillation. Dynamic scaffolds also offer the advantage of changing shape after implantation, allowing for small, easily implantable scaffolds that can grow to fill a tissue defect while preserving the ability to guide cells toward the desired lineage. As shape memory polymer technology continues to advance, it offers a promising means to mimic the dynamic ECM further and regulate cell response in other cell lines and differentiation pathways.

Incorporating Biomimetic Factors into Synthetic Scaffolds

While fiber parameters can drive cell responses, a limitation of synthetic polymer scaffolds is the lack of cell signaling cues provided by the native ECM. Therefore, tissue engineering commonly incorporates proteins and other biomimetic factors from the ECM into synthetic polymer scaffolds to provide additional cell signaling cues to the enhanced structural and architectural cues provided by synthetic scaffolds. These biomimetic factors are incorporated through various means: coating a scaffold, covalently linking to the scaffold, or by adding nanoparticles to the system that release the biomimetic factors over time. In all cases, the addition of biomimetic factors seeks to further enhance and guide cell response to the desired end.

Incorporating growth factors and other biomimetic molecules into the fiber system is commonly used to further induce differentiation using various strategies. Coating poly(L-lactic acid) (PLLA) electrospun fibers with polydopamine induced osteogenic differentiation in hMSCs, with greater expression of ALP, RUNX2, bone sialoprotein, and interleukin 8 on the polydopamine-coated fibers than on the uncoated fibers – both scaffolds with comparable fiber parameters. Adding hydroxyapatite and graphene oxide to electrospun PLGA fibers increased ALP activity, RUNX2, and OPN expression, calcium deposition, and cell proliferation in mouse MC3T3-E1 pre-osteoblast cells, but also decreased the fiber diameter of the scaffolds from 1.35mm to 885 nm. As smaller fiber diameters also promote osteogenic differentiation, this decrease in fiber diameter could equally have affected the increased osteogenic gene expression. The addition of graphene oxide to the fibers increased their tensile strength two-fold. The increased mechanical properties could be the mechanism leading to the increased osteogenic expression, as high substrate elasticity and stiffness guide cells toward osteogenic lineages [169-173].

The effect of transforming growth factor beta 3 (TGF-β3) in culture medium depended on fiber alignment: on aligned fibers (4o angular deviation; 5.2 μm fiber diameter; 76% porosity), TGF-β3 induced chondrogenesis in hMSCs via increased COL2A1, ACAN, and SOX9 expression, whereas TGF-β3 induced osteogenesis in hMSCs (increased BMP2, RUNX2, and COL1A1 expression) on randomly aligned fibers (5.1 μm fiber

diameter; 79% porosity). Aligned fibers coated with connective tissue growth factor increased tenomodulin expression inducing ligamentous or tenogenic differentiation of hMSCs. Incorporation of nanoparticles (~150 nm) containing platelet-derived growth factors (PDGF) into aligned collagen fibers increased tenomodulin and scleraxis expression in rASCs, with no effect on unwanted ALP activity or osteocalcin production [174,175]. However, the PDGF-nanoparticles did not increase ostenogenic expression in rASCs cultured on randomly oriented fibers. While PDGF was found to improve tenogenesis on aligned collagen fibers but not randomly oriented fibers, the fiber diameters and porosity were not investigated or controlled.

Bio printing is yet another method to include growth factors to influence differentiation. Aligned nanofibers promote osteogenesis, tenogenesis, and myogenesis depending on cell type. Bioprinting growth factors onto polystyrene STEP fibers (~668 nm fiber diameter; angular deviation of 2.5o) modulated cell fate: C2C12 cells differentiated toward tenogenic lineages on regions coated with fibroblast growth factor 2, toward osteogenic lineages in regions coated with bone morphogenic protein (BMP)- 2, but toward myogenic lineages in uncoated regions. Incorporation of proteins into the fiber system also enhances differentiation. Human aortic SMCs did not proliferate on randomly oriented or aligned polyurethane nanofibers, but the addition of collagen into the fibers increased SMC proliferation [176,177]. However, while the fibers were nanofibers in both cases, the polyurethane:collagen-blend fibers had a decreased fiber diameter (~200 nm vs. ~400 nm) and decreased pore size (~300 nm vs. ~700 nm), which could have promoted proliferation but it was not controlled for. Blended PLLA/type I collagen (4:1 ratio) nano fibers led to increased type I, II, and X collagen, and decorin expression at 4 days. However, the PLLA/type I collagen fiber diameters (238 nm) were lower than the PLLA-alone fibers (750 nm), which could affect the gene expression, but was not investigated.

Many biological tissues exhibit endogenous electric fields, which have been characterized during development and regeneration. Cartilage and bone exhibit piezoelectric behaviour during loading, but piezoelectric biomaterials remain relatively unexplored in tissue engineering [178-180]. Recently, however, electrospun fibrous scaffolds composed of piezoelectric material were designed and investigated in the chondrogenesis and osteogenesis of hMSCs. Piezoelectric fibers (5.9 μm fiber diameter; 93% porosity) with a low voltage output produced an electric field that (20 mV/mm) promoted chondrogenesis while electrospun PCL (9.8μm fiber diameter; 88% porosity) scaffolds could not.

Alternatively, piezoelectric fibers (6.9mm fiber diameter; 92% porosity) with a high voltage output produced electric fields that (1 V/mm) promoted osteogenesis compared to the low voltage piezoelectric fibers and the PCL fibers. The electric fields, along with mechanical stimulation, improved differentiation compared to mechanical loading alone. Coating aligned, electrospun nanofibers with fibronectin improved neurite extension in NG108-15 neuroblastoma and glioma cells compared to the uncoated fibers hMSCs elongated on polydopamine-coated fibers – even on randomly oriented fibers where they normally form rounded morphologies. hMSCs demonstrated greater spreading, enhanced adhesion, and robust focal adhesion formation on polydopamine-coated fibers compared to uncoated fibers. Human skeletal muscle myoblasts and fibroblasts elongated on nanofibers coated with laminin or collagen while they exhibited polygonal morphology on the uncoated fibers. Porous electrospun fibers enhanced PC12 cell adhesion. L929 cells protruded more pseudopodia, and many filopodia anchored into the pores, suggesting porous fibers can enhance cell adhesion [181-183]. NIH 3T3 fibroblasts aligned more with larger, aligned PLGA fibers (740 nm diameter) than with smaller, aligned fiber (140 nm diameter). On the larger fibers, the cells' filopodia continuously sampled other fibers, but their lamellipodia extended primarily along single fibers. On the smaller fibers, however, the fibroblasts' lamellipodia extended along many directions when their filopodia contacted misaligned fibers, likely due to the decreased adhesion sites on the smaller fibers. Indeed, when the PLGA fibers were treated with poly(L-lysine) to improve cell adhesion, the fibroblasts' alignment significantly increased – especially on the smaller fibers – suggesting that more stable focal adhesion complexes guide cell alignment.

Mouse E13 NSCs' migration distance on fibers coated with poly-D-lysine depended on fiber diameter, while coating the fibers with laminin induced promoted migration regardless of fiber size. NSC neurospheres migrated radially outward equidistantly on laminin-coated nanofibers (860 nm) but extended along the direction of the fibers on laminin-coated microfibers (8.8 μm). In 3D culture, HT-1080 fibrosarcoma cells traveled long distances, rapidly and persistently, while maintaining high protrusion formation rates on low collagen densities that had increased alignment and pore sizes (1 mg/mL). Cell migration slowed on intermediate collagen densities (decreased fiber alignment and pore size compared to the low-density collagen fibers) but then increased on higher collagen densities (6 mg/mL) despite no significant changes in fiber alignment or pore size compared to the intermediate collagen densities. The opposite response occurred for 2D cell motility with increasing ligand density. This same biphasic pattern arose in MDA-MB-231 cells. Crosslinking the collagen reduced cell migration speed without altering the collagen gel density, adding further evidence that fiber alignment is a significant factor in cell migration, even with biomimetic factors. Topographical cues from fiber alignment dominated HUVEC motility over a chemical gradient of vascular endothelial growth factor orthogonal to fiber alignment but had an additive effect when the two were parallel [184-186]. Fiber diameters and porosity were not reported in the study, but the fibrous scaffolds were electrospun using the same parameters and should have similar architecture.

The literature demonstrates that fibers drive many cellular responses. In native ECM, the fibrous proteins provide signalling cues to drive cell differentiation, proliferation, adhesion, and migration. Tissue engineering controls the fiber parameters of scaffolds to regulate cell response during engineered development. Fiber diameter regulates differentiation in a lineage-dependent manner: nanofibers drive osteogenesis, fiber diameter has a biphasic effect on chondrogenesis, the effect of fiber diameter on tenogenesis changes over time, and differing fiber diameters can drive cells toward specific neural lineages.

Larger fiber diameters lead to greater cell elongation and alignment. Cells migrate at higher speeds on smaller fibers, while they migrate farther distances on larger fibers. Increased fiber alignment can drive cells into tenogenic, cardiomyogenic, and neuronal lineages, while non-aligned fibers guide cells toward osteogenic and glial differentiation. Cells elongate and align with underlying fibers, forming a spindle shape morphology on aligned fibers, while they form a rounded morphology on randomly oriented fibers. Therefore, aligned fibers appear to provide a cellular 'highway': cells migrate along the direction of aligned fibers and migrate faster on aligned fibers. Cells will follow aligned fibers preferentially across chemotactic gradients. Low scaffold porosity, or high fiber density, leads to greater cell proliferation [187].

Porosity also guides differentiation into multiple cell lineages as a function of pore size and shape. When the pores are small, cells can extend across multiple fibers, leading to a more rounded morphology and lower migration speed. Conversely, when the pores are large, cells will attach and align with single fibers, which also results in increased migration speeds. While synthetic fibers can drive these responses, incorporating biomimetic factors into the scaffolds can further improve the desired response and modulate the response via interactions with the scaffold structure and architecture. Cells tend to align and elongate along microfibers and aligned fibers through common intracellular mechanisms. Commonly on both microfibers and aligned fibers, cells formed larger or greater numbers of focal adhesions along the increased cell-contact area. This also occurred in cells along large pores (i.e., essentially along a 'single fiber' in all cases). The increased focal adhesions lead to the actin cytoskeleton.

Conclusion

After a critical review of exemplary recent research works on cell-free fiber based scaffolds for in situ TE, including clinical studies, it has been concluded that in order to make use of the whole range of favors which may be provided by engineered fibrous scaffold systems, there are four main issues which need to be addressed:

1. Logical combination of manufacturing techniques and materials.
2. Biomaterial fiber development.
3. Adaption of textile manufacturing techniques to the demands of scaffolds for regenerative medicine.
4. Incorporation of biological cues (e.g. stem cell homing factors).

Several key parameters such as physiochemical characteristics of fibers, pore size and mechanical properties of the fabrics play important role in the effective use of textile technologies in tissue engineering. This review summarizes the current advances in the manufacturing of biofunctional fibers. Different textile methods such as knitting, weaving, and braiding are discussed and their current applications in tissue engineering are highlighted.

Therefore, this review examines fibrous proteins of the extracellular matrix and their effects on cell behavior, followed by a discussion of the cellular responses elicited by fiber diameter, alignment, and scaffold porosity of two dimensional (2D) and three dimensional (3D) synthetic scaffolds. Variations in fiber diameter, alignment, and scaffold porosity guide stem cells toward different lineages. Cells generally exhibit rounded morphology on nanofibers, randomly oriented fibers, and low-porosity scaffolds. Conversely, cells exhibit elongated, spindle-shaped morphology on microfibers, aligned fibers, and high-porosity scaffolds. Cells migrate with higher velocities on nanofibers, aligned fibers, and high-porosity scaffolds but migrate greater distances on microfibers, aligned fibers, and highly porous scaffolds. Incorporating relevant biomimetic factors into synthetic scaffolds destined for specific tissue application could take advantage of and further enhance these responses.

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