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Fiber-Based Tissue Engineering: Progress, Challenges, and Opportunities

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Abstract

Tissue engineering aims to improve the function of diseased or damaged organs by creating biological substitutes. To fabricate a functional tissue, the engineered construct should mimic the physiological environment including its structural, topographical, and mechanical properties. Moreover, the construct should facilitate nutrients and oxygen diffusion as well as removal of metabolic waste during tissue regeneration. In the last decade, fiber-based techniques such as weaving, knitting, braiding, as well as electrospinning, and direct writing have emerged as promising platforms for making 3D tissue constructs that can address the above mentioned challenges. Here, we critically review the techniques used to form cell-free and cell-laden fibers and to assemble them into scaffolds. We compare their mechanical properties, morphological features and biological activity. We discuss current challenges and future opportunities of fiber-based tissue engineering (FBTE) for use in research and clinical practice.

Keywords

Tissue Engineering; Fiber-based techniques; Scaffold fabrication; Cell-laden constructs

1. Introduction

In the past decades, tissue engineering has emerged as a multidisciplinary field encompassing medicine, biology, and engineering in which researchers utilize various tools

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to fabricate tissue-like biological constructs (Berthiaume et al., 2011). Such constructs should mimic the physiological environment including the structural, physical, and topographical features of the native tissues (Khademhosseini et al., 2009). In addition to the ultimate goal of replacing diseased and damaged organs in human body, engineered tissues can be used for diagnostic and therapeutic research.

Tissue engineering methods can be divided into “top-down” and “bottom-up” approaches (Figure 1). Top-down strategies rely on a scaffold, typically a porous biocompatible and/or biodegradable structure that is seeded by cells and incubated in suitable culturing conditions until the cells proliferate and form an extracellular matrix (ECM) that resembles the native tissue (Nichol and Khademhosseini, 2009). Bottom-up methods rely on small, cell-laden modules (building blocks) that are assembled into larger constructs. These methods better mimic the native biology of some organs that have repetitive modules such as liver (Moon et al., 2010, Wilson and Boland, 2003)

For the top-down approach, various methods have been developed to fabricate porous scaffolds. Scaffold fabrication methods include nanofiber self assembly (Lutolf and Hubbell, 2005), emulsion freeze-drying (Ho et al., 2004), gas foaming (Chung et al., 2011, Harris et al., 1998, Wang et al., 2006a), solvent casting and particle leaching (Katoh et al., 2004, Nam and Park, 1999, Park et al., 2007, Tan et al., 2005, Vogelaar et al., 2003, Wiria et al., 2007), computer-aided design/computer-aided manufacturing (CAD/CAM) technologies (Gauvin et al., 2012, Hollister, 2005), and fiber-based techniques (Heinemann et al., 2009, Lei and You-Lo, 2005). The assembling techniques for bottom-up fabrication include additive photo crosslinking of cell-laden hydrogels (Liu and Bhatia, 2002, Tan and Desai, 2004), packing of cell encapsulated modules (Chan et al., 2010), directed assembly of modules (Zamanian et al., 2010), cell sheet methods (L’Heureux et al., 2006), and fiber-based techniques (Fedorovich et al., 2010, Ghorbanian et al., 2009) as well.

Artificial fibrous structures in the form of textiles can be traced back several millennia and were used as clothing and decoration. In the past century, fiber-based techniques have been widely used in numerous engineering applications such as filtration, composite fabrication, energy systems, and microfluidics (Safavieh et al., 2011, Tamayol et al., 2012). The microstructure of the fabricated constructs can be tuned to optimize their mechanical and transport properties (Tamayol and Bahrami, 2011). Recently, fiber-based techniques, which include textile technologies, electrospinning, and direct writing, have been applied for the fabrication of 3D scaffolds and cell-laden constructs in tissue engineering (Moutos et al., 2007). Scaffold fabrication based on nanofiber self assembly method is not considered in this review; critical reviews on this technique are available elsewhere (Ma et al., 2005, Zhang, 2003).

In this review, we describe various fiber fabrication techniques, which have been used in tissue engineering. This includes the recent developments in the fabrication of cell-free and cell-laden fibers with controlled geometries, shapes and mechanical properties. We also review different methods of assembling fibers along with their advantages and limitations in tissue engineering applications. We compare their mechanical properties, morphological features and biological activity. Finally, we discuss current challenges and future opportunities of fiber-based tissue engineering for use in research and clinical practice.

2. Fiber formation techniques

Various approaches exist for fabricating fibers from naturally-derived or synthetic materials for tissue engineering applications; these approaches include: i) electrospinning, ii) wetspinning, iii) biospinning, iv) interfacial complexation, v) microfluidic spinning, and vi)

meltspinning (extrusion) (Figure 2). In the following sections, we describe these techniques along with their advantages and weaknesses.

2.1 Electrospinning

In electrospinning, fibers are drawn by the flow of a viscoelastic polymer subjected to an applied electric field between an injecting needle and a collector plate in a distance from the needle (Deng et al., 2012, Mauck et al., 2009). Mats with randomly oriented or aligned fibers can be formed by using a stationary or a rotating collector, respectively. Fibers with diameters in the range of 100 nm to few micrometers can be created depending on the polymer physical properties (e.g., viscosity, electrical conductivity and surface tension), applied electric field, polymer flow rate, and the distance between the needle tip and the collector, (Zussman, 2011).

The strengths of electrospinning for scaffold fabrication are: i) relative simplicity; ii) efficient control over the key process parameters such as flow rate and voltage; and iii) the possibility to scale-up (Deng, James, 2012). The process, however, has difficulty in manufacturing of thick 3D complex scaffolds which are desirable for many applications (Hwang et al., 2008). Moreover, the fiber packing density is relatively high and hard to control, resulting in small pore sizes (~10–15μm) that limit cell infiltration into the scaffolds (Leong et al., 2010, Shabani et al., 2012). The latter issue has triggered an array of techniques including salt/polymer leaching (Lee et al., 2005), wet electrospinning using a bath collector (Yokoyama et al., 2009) or an ice crystal collector (Simonet et al., 2007), and laser/UV irradiation (woon Choi et al., 2007) to produce electrospun scaffolds with both large pores and high porosity.

Encapsulation of living cells in electrospun fibers have been demonstrated in several studies (Lopez-Rubio et al., 2009, Shih et al., 2012, Townsend-Nicholson and Jayasinghe, 2006). This has been achieved by using a coaxial needle configuration with each needle connected to a syringe pump providing constant flow rates. The encapsulation of living cells in electrospun fibers faced many challenges as the diameter of the fibers is typically smaller than a single cell (Lopez-Rubio, Sanchez, 2009, Townsend-Nicholson and Jayasinghe, 2006). Another shortcoming of the electrospinning of cell encapsulated constructs is the lack of control over cell distribution in the volume. Moreover, high electric fields (~ 1–2 kV/cm) may harm the cells, thus, further investigations on the cell viability should be performed.

2.2 Wetspinning

In Wetspinning, fibers are formed by injecting a pre-polymer solution into a coagulation bath where it continuously polymerizes so as to form a long fiber. The coagulation bath must be either a poor solvent or a non-solvent with respect to the polymer (Puppi et al., 2011). The flow of polymer solution can be produced manually (Enea et al., 2011, Kato et al., 1989), or using syringe pumps (Puppi, Dinucci, 2011, Spinks et al., 2006), or by applying pressure (Arumuganathar and Jayasinghe, 2008, Arumuganathar et al., 2007, Jayasinghe and Suter, 2010). Wetspinning is a well-established technique that can produce fibers with a wide a range of diameters from ~30 to 600 μm (Lee et al., 2011b). Wetspun fibers have been made, from alginate, collagen-alginate composite (Lee et al., 2011a), collagen (Enea, Henson, 2011), chitosan (Tuzlakoglu et al., 2004), polycaprolactone (PCL) (Puppi, Dinucci, 2011), starch-PCL composite (Leonor et al., 2011), chitosan-tripolyphosphate composite (Pati et al., 2012), and calcium phosphate cement-alginate composite (Lee, Lee, 2011a). These fibers were used to make a variety of fiber-based tissue analogs of cartilage (He et al., 2012, Neves et al., 2011), tendon and ligament (Enea, Henson, 2011), bone (Lee, Lee, 2011a, Puppi, Dinucci, 2011), and neural tissues (DeRosa et al., 2011). The diameter of fibers can be tuned by changing the needle(s) diameter, the

polymer composition, and its volumetric flow rate (Fedorovich, Moroni, 2010, Lee, Lee, 2011a). The mechanical strength of the fibers can be increased by orders of magnitude by adding carbon nanotubes (CNTs) (Spinks, Shin, 2006) or graphene oxide (He, Zhang, 2012) to the pre-polymer solution.

Scaffolds can be made by wetspinning fibers and randomly depositing them on a substrate (Lee, Lee, 2011a, Lee, Park, 2011b, Leonor, Rodrigues, 2011, Pati, Adhikari, 2012, Puppi, Dinucci, 2011) or by rolling them up (Landers et al., 2002), as with electrospinning. Since the fibers fabricated with wetspinning are relatively thick, the pore size of the formed scaffolds is large (~250–500μm) (Neves, Moreira Teixeira, 2011), and as they are deposited in a solution, the scaffolds tend to have a much higher porosity (up to 92%) (Pati, Adhikari, 2012), compared to those formed by dry electrospinning. These features help cell adhesion, proliferation, and penetration within the inner part of the scaffold (Puppi, Dinucci, 2011).

Cell-laden fibers were made using alginate because the prepolymer solution, the gelation agent and the coagulation bath are all compatible with live cells. Arumuganathar *et al.* formed cell-laden fibers using a three-needle pressure-assisted system to fabricate multi-compositional structures that carried living cells in an inner layer (Arumuganathar and Jayasinghe, 2007b). The encapsulating medium flowed in the outer needle and provided a sheath for the suspension layer. (Arumuganathar et al., 2008, Arumuganathar and Jayasinghe, 2007a, Arumuganathar and Jayasinghe, 2007b).

Wetspinning is a simple method that can be used to form fibers from different materials for FBTE. However, cell-laden fibers have mostly been fabricated using calcium alginate. Long exposure to chemicals during the fabrication process can be harmful to cells. Although electrospinning is more widely used, wetspinning has several advantages such as intrinsic higher porosity and larger pore size.

2.3 Microfluidic spinning

Microfludic spinning is defined here as the formation of fibers in a microchannel using a coaxial flow of a pre-polymer and a cross-linking agent. This is similar to wetspinning, except that the cross-linking agent is supplied by the coaxial flow directly instead of the bath. To prevent polymerization inside of the system, the streams need to be coaxed close to the nozzle, which can be achieved using microfluidic systems made by microfabrication. The short distance of coaxial flow facilitates the formation of cell-laden fibers as the cells because the channels are short and hence the cells are only briefly exposed to a high shear stress.

Microfluidic spun fibers have been formed using various polymers such as alginate (Mazzitelli et al., 2011, Su et al., 2008, Yamada et al., 2012), chitosan, poly(lactic-co-glycolic acid) (PLGA) (Hwang et al., 2009, Hwang, Khademhosseini, 2008), and chitosan/alginate (Lee, Lee, 2011a). A rotating roller can be used to collect the fabricated fibers and to form scaffolds containing aligned fibers (Hwang, Park, 2009, Hwang, Khademhosseini, 2008, Su, Zheng, 2008). The diameters of the fabricated fibers can vary from ten to several hundreds of micrometers, depending on parameters such as flow rates of core and sheath solutions, channel dimensions, and solutions viscosities (Hwang, Park, 2009). The rotation speed of the collecting roller may also affect the fiber diameter as it imposes an external elongation stress on the fiber (Kang et al., 2011).

Incorporation of living cells in fibers fabricated using microfluidic spinning systems has been demonstrated by several researchers (Hwang, Park, 2009, Lee, Lee, 2011a, Mazzitelli, Capretto, 2011, Shin et al., 2007, Su, Zheng, 2008, Yamada, Sugaya, 2012). For example, Shin *et al.* encapsulated human fibroblast cells in calcium alginate fibers and demonstrated

that the cells remained viable after seven days of culture. In another study, Sue *et al.* diluted fluorescent polystyrene microspheres with the diameter of 0.75 μm, *E. Coli*, and yeast cells in alginate solution and passed them into a calcium chloride ($CaCl_2$) bath through a polydimethylsiloxane (PDMS) microchannel to form cell-laden fibers (Su, Zheng, 2008). Lee *et al.* also adopted a microfluidic spinning technique to encapsulate human hepatocellular carcinoma (HepG2) cells within chitosan-alginate fibers (Lee, Lee, 2011a). They found that the bi-component fibers offer a better cell viability than pure alginate fibers. Mazzitelli *et al.* fabricated a glass-based microfluidic chip consisted of three inlets and three dispersing chambers for co-encapsulation of cells and drugs in fibers (Mazzitelli, Capretto, 2011). Their system can be used for better regulation of cell differentiation in a precisely 3D configuration.

Among the benefits of using microfluidic spinning is that the microfluidic systems allow for additional control mechanisms and multiplexing in the fiber fabrication. For example Kang *et al.* developed a microfluidic chip that mimicked silk-spinning process of spiders (Kang, Jeong, 2011). . (Kang, Jeong, 2011) (Figure 3b–d). This shows the robustness of the design for fabrication of cell-laden fibers for tissue engineering. Yamada *et al.* fabricated a PDMS-based microfluidic system to continuously synthesize chemically and physically anisotropic calcium alginate fibers (Yamada, Sugaya, 2012). Their microfluidic chip consisted of seven inlets and one main straight gelation channel. Cell suspension solution of sodium alginate, buffer solution, and $CaCl_2$ solution were fed into the chip using syringe pumps. Cell-laden fibers were collected by a rotating roller that was partially dipped in a bath of $CaCl_2$. They added polyglycolic acid (PGA) to the alginate solution to adjust the stiffness of the local region of the alginate fibers and form sandwich-type solid-soft-solid structures, which provides better control on the direction of cell proliferation and networking.

Microfluidic spinning method is a promising platform for continuous fabrication of fibers with tunable morphological, structural, and chemical features. In general, the size of the fibers fabricated with microfluidic systems is smaller than wetspun but larger than electrospun fibers. However, the biopolymers that are currently in use cannot form mechanically strong fibers to be used with conventional textile systems. Lee *et al.* reported the tensile strength of 0.66 MPa and 0.85 MPa for calcium alginate and chitosan-alginate composite fibers, respectively (Lee, Lee, 2011a). Moreover, since the process of fiber fabrication is relatively slow, creating 3D structures is time consuming.

2.4 Biospinning

The process of silk fiber fabrication by insects is defined as biospinning (Mandal and Kundu, 2010). Silk has been used for FBTE for many years and its natural source is the cocoon and nets produced by various insects such as silkworm and spider. Silk is well known for its high tensile strength while it is also biodegradable. In addition, following chemical processing, it is non-cytotoxic and non-inflammatory. (Acharya et al., 2008, Cao and Wang, 2009).

Morphology and tensile properties of silks produced by different families of insects such as cecropia *(Hyalophora cecropia)* moth (Reddy and Yang, 2010), tasar silkworms, *bombyx mori* silkworms (Cunniff et al., 1994, Pérez-Rigueiro et al., 2000), and spiders (Cunniff, Fossey, 1994) have been investigated by several researchers. It has been shown that the silk fibers comprise a core made of fibrous protein (fibroin) surrounded by a glue protein (sericin) (Dash et al., 2007, Dash et al., 2006). Fibers are drawn directly from immobilized insects, and depending on how they are drawn, different diameters can be produced. For example, the fiber diameter could range from 25 μm to 30 μm and from 65 μm to 70 μm for manually drawn and naturally spun cocoons, respectively (Mandal and Kundu, 2010). 3D structures of biospun fibers have been shown to have high porosities with the pore sizes

ranging from 100 μm to 500 (Mandal and Kundu, 2010). In addition, the silk fibers fabricated by biospinning have relatively high tensile strengths (~460–972 MPa),

Biospun fibers are suitable for load bearing tissue engineering applications (e.g. tendon or bone) where high mechanical strength, ~ 150 MPa, is required (Gosline et al., 1999). The major challenges facing the use of biospun fibers in FBTE are: i) the limitation of resources, which make the scale-up process questionable; ii) the time consuming and expensive preprocessing and handling of natural silk fibers; iii) the lack of control over the size of the fabricated fibers; and iv) the current impossibility of incorporating cells in the fibers.

2.5 Interfacial complexation

Interfacial complexation technique includes the fabrication of fibers at the interface of two oppositely charged polyelectrolyte solutions by means of poly ion complex (PIC) formation (Decher, 1997, Ohkawa et al., 2002). In this technique, two oppositely charged polyelectrolyte droplets are placed in close proximity. The contact interface is then drawn upward by means of a forceps or a bent needle to fabricate a solid fiber (Wan et al., 2004). Continuous fibers have been fabricated by means of a speed-controlled mechanical roller from various polyelectrolyte solutions such as chitosan, sodium alginate, and hyaluronic acid (Lim et al., 2006, Wan, Liao, 2004, Yim et al., 2006). Fibers formed by this method usually consist of primary fibers, which are composed of parallel ridges, valleys and beads spaced out at regular intervals along the fiber axis (Wan, Liao, 2004). Depending on the two polyelectrolyte concentrations and the interfacial area, the diameter of fabricated fibers can vary from 10 μm to 20 μm (Tai et al., 2010, Wan, Liao, 2004, Yim, Wan, 2006) and the tensile stress can change in the range of 20–200 MPa (Ohkawa, Ando, 2002, Yim, Wan, 2006).

The interfacial complexation fiber process can be used to encapsulate cells or particles at ambient temperature and under aqueous conditions. For example, Wan *et al.* fabricated particle-laden fibers by dispersing silica gel beads in an alginate solution and drawing the fiber at the interface of the alginate and a purely aqueous chitosan solution (Wan, Liao, 2004). They showed that the viscosity of the alginate solution increased as more beads were added to the solution, thus thicker fibers were obtained. In another study, Yim *et al.* used a similar approach to encapsulate human mesenchymal stem cells (hMSCs) in polyelectrolyte complexation (Yim, Wan, 2006). They showed that the fabricated fibers could support the proliferation and differentiation of hMSCs encapsulated within the fibers.

Despite the simplicity of this technique, large scale fiber drawing is hard to achieve, which limits its application to lab-scale systems. Moreover, this technique is restricted to a few materials and the range of the fabricated fiber diameters is limited. Since the fiber diameters fabricated by interfacial complexation are generally close to the one of a cell, fabrication of smooth cell-laden fibers is challenging.

2.6 Meltspinning (extrusion)

In the meltspinning process, a polymer is heated to its melting point and is extruded through a spinneret to form continuous fiber strands. This technique has been used to create fibers from various synthetic polymers such as polyethylene terephtalate (PET) (Lu et al., 2005, Sinclair et al., 2010), starch–PCL and starch–poly(lactic acid) (PLA) (Gomes et al., 2008), PLA (Chester and Bornemann, 2008, Ellä et al., 2011, Lu, Simionescu, 2005, Sumanasinghe et al., 2010), and poly(3-hydroxybutyrate) (Chester and Bornemann, 2008, Hinüber et al., 2010). Meltspinning process enables customized fiber constructions including monofilament (Sumanasinghe, Haslauer, 2010), multifilament (Ellä, Annala, 2011), and low denier per filament (DPF) (Sinclair, Webb, 2010) with the ability to create complex cross-sections. For

example, fractal-like (Lu, Simionescu, 2005, Sinclair, Webb, 2010) or hollow fibers (Hinüber, Häussler, 2010) have been created to enable cell alignment and topographical control of cell orientation. Fibers fabricated by meltspinning have relatively high mechanical properties with ultimate tensile strength of ~340 MPa and elastic modulus of 7.1 GPa (Chester and Bornemann, 2008). Therefore, meltspun fibers are suitable for textile based fabrication techniques such as knitting, weaving, or braiding (Ellä, Annala, 2011).

Meltspinning process usually requires high temperature in range of 150 °C to 295 °C (Gomes, Azevedo, 2008, Sinclair, Webb, 2010) and the use of expensive equipments. Since the melted polymers are usually highly viscous (e.g., viscosity of PLA at melting point is 10^4 times higher than water (Ajioka et al., 1995)), high pressures are required to push the polymer through the spinneret (Akbari et al., 2011). Mass loss and a rapid decrease of viscosity during the process are other challenges that often have considerable influence on the mechanical properties of the resultant fibers (Fakirov and Bhattacharyya, 2007). In addition, the high temperatures used during the fabrication process prevent the formation of cell-laden fibers and limits protein loading for the controlled delivery of bioactive molecules to promote tissue formation. In general, fibers larger than a few micrometers can be fabricated with meltspinning. In addition, the cross-section of meltspun fibers and their texture can be tailored. This feature can be beneficial for applications were the fiber texture is important for orientating the cells.

3. Fiber-based techniques for scaffold fabrication

Fiber-based technologies including textile techniques, electrospinning, and direct writing are suitable for fabrication of complex tissue-like constructs (Figure 4). Conventional textile techniques such as weaving, knitting, and braiding have been used to form porous constructs with structural and mechanical properties similar to native tissues (McCullen et al., 2010). These structures can serve either as tissue scaffolds or as reinforcements within cell-laden hydrogels to improve their mechanical stability. Recent development in fabricating fiber reinforcement have been reviewed by McCullen *et al.* (McCullen, Haslauer, 2010). Another fiber-based technique for the formation of complex tissue constructs is direct writing. Tissue engineering writers are usually programmable and controlled by computers. Writing techniques can form complex structures with a high resolution and reliable precision (Fedorovich, Moroni, 2010).

We discussed electrospinning techniques in Sec. 2.1. In this section, we will review recent achievements in using textile techniques and direct writing technologies for fabricating tissue engineering scaffolds. Also, a selection of existing studies that employed fiber-based techniques to create biomimetic fibrous tissue scaffold is listed in Table 1.

3.1 Weaving

Weaving is a textile technique in which two distinct sets of warps or wefts are interlaced at right angles to form a fabric with controlled strength, porosity, morphology, and geometry. Woven structures are lightweight, strong, and flexible. In the past decades, weaving techniques have been employed to fabricate 3D constructs (Zheng ming, 2000). Regular woven structures have fibers in only two dimensions; exhibiting poor resistance towards forces applied in the through-plane direction. To solve this problem, different layers have been connected either layer-to-layer or by interlocking all the layers (Kamiya et al., 2000). In addition, woven fabrics show a low shear resistance in the in-plane direction (Kamiya, Cheeseman, 2000). Comparison between the mechanical properties of scaffolds produced by different weaving strategies have been discussed in details elsewhere (Kamiya, Cheeseman, 2000).

A microscale weaving technology was developed by Guilak and his coworkers to create 3D PGA woven scaffolds with mechanical properties similar to native articular cartilage (Figure 5) (Moutos, Freed, 2007, Moutos and Guilak, 2008, 2010a). Multiple layers of perpendicular fibers were woven in the in-plane direction and interlocking fiber were passed through-the-thickness to lock all layers in place. Recently, Abrahamsson *et al.* fabricated 3D woven PCL scaffolds and seeded them with hMSCs suspended in collagen gel for osteochondral tissue engineering (Abrahamsson et al., 2010).

3.2 Knitting

In knitting, a fabric is formed by intertwining yarns or threads in a series of connected loops. Kintted yarns in contrast to woven fabrics with straight threads, form symmetric loops (Wang et al., 2011). Knitted textile substrates include fibers in the through-plane directions. Thus, they offer a higher through-plane mechanical properties in comparison with other textile based constructs (e.g. woven and braided structures), but they are weaker in the in-plane direction (Pandita et al., 2002). Knitted structures usually have a higher porosity but a lower thickness than woven substrates (McCullen, Haslauer, 2010). Various knitting techniques and their applications in tissue engineering are reviewed by Wang *et al.* (Wang, Han, 2011). As a result of their suitable mechanical properties and ease of fabrication, knitted fabrics have found several applications in medicine for example as surgical mesh in repairing hernia (Boukerrou et al., 2007, Jacobs et al., 1965), pelvic organ prolapse (Altman et al., 2008, Ganj et al., 2009), pelvic floor dysfunction (Ostergard, 2011), as well as endovascular prosthetic devices (Freitas et al., 2010). A number of knitted surgical meshes such as TIGR® Matrix (Novus Scientific, San Diego, CA), PROCEED™, ULTRAPRO* (Ethicon Inc., Somerville, NJ), Bard® Mesh (Bard Davol Inc., Warwick, RI) are now commercially available, which are approved by the US food and drug administration (FDA) for the abovementioned applications. Knitted structures have been also used as scaffolds or reinforcements in composite scaffolds for engineering various tissues such as cartilage (Dai et al., 2010, Kawazoe et al., 2010), ligaments and tendons (Sahoo et al., 2007), skin (Ananta et al., 2008, Wang et al., 2012b, Zhong et al., 2010), and blood vessels (Ravi and Chaikof, 2009).

Knitted structures have been combined with other materials to improve their mechanical and biochemical properties. For example, a 3D hybrid scaffold for cartilage regeneration was fabricated by incorporating a type I collagen within a PLGA knitted mesh to improve cell adhesion (Chen et al., 2005, Dai, Kawazoe, 2010) (Figure 5). In a notable study, Sahoo *et al.* compared the mechanical properties of different scaffolds fabricated from knitted PLGA fibers; knitted PLGA fibers coated with electrospun PLGA, collagen, and PCL nanofibers; and woven PLGA fibers over a period of 4 weeks of incubation (Sahoo, Cho-Hong, 2007). The woven structure showed the highest tensile strength and elastic modulus compared to other scaffolds. The mechanical properties of all knitted scaffolds were identical with the exception of non-coated PLGA fiber, which offered a higher elastic modulus. Among all the fabricated scaffolds, seeded by bone marrow stromal cells (BMSC), hybrid scaffolds exhibited higher cell attachment.

In another study, Sahoo *et al.* knitted scaffolds from *Bombyx mori* silk threads and subsequently filled the pores of resultant scaffolds with electrospun PLGA nanofibers (Sahoo et al., 2010). Xu *et al.* also knitted polyester filaments in a circular pattern around a glass mandrel (Xu et al., 2010). The knitted structures were used to reinforce polyurethane vascular graft. It was shown that the strength and elasticity of grafts made of composites was higher than the ones made of pure polyurethane. Ananta *et al.* knitted poly(lactic acid-co-caprolactone) (PLACL) fibers that were infiltrated with type I collagen by a plastic compression process of two separate collagen slabs (Ananta, Aulin, 2008). The fabricated

scaffolds supported the migration and growth of neonatal fibroblasts within the 3D structures.

Embroidered constructs can also be formed by connected loops. The difference between embroidered and knitted structures is that in the former, each loop can be connected to several other loops. Embroidered patches have been used as scaffolds for bone tissue engineering as they can tolerate tensile, compressive, and bending forces. (Rentsch et al., 2010). Rentsch *et al.* employed a computer aided embroidery machine to fabricate PCL scaffolds. Some of the scaffolds were coated with Collagen I or a composite of chondroitin sulfate and then seeded with hMSC for bone tissue engineering (Figure 6) (Rentsch et al., 2009). The scaffolds allowed cell adhesion and proliferation. HMSC-seeded scaffolds cultured in the presence of osteogenic supplements, showed enhancing alkaline phosphatase activity for 14 days and produced calcified matrix after 28 days.

Knitted constructs offer adequate and tunable mechanical properties as well as easy fabrication of 3D geometries, which have made them popular for various tissue engineering applications. In addition, the pore size of the constructs can be varied over the area and volume of the scaffold to adjust its physical and mechanical properties, which make it attractive for use as connective tissues for example.

3.3. Braiding

In braiding, complex structures or patterns are formed by intertwining three or more fiber strands, which allows making cylinders and rods suitable for engineering connective tissues and blood vessels notably. In comparison with knitted structures, braided stents for arterial implants showed a higher resistance in radial compression (Freitas, de Araujo, 2010). In general, the porosity of the braided fabrics is lower than their knitted counterparts. Multistep braiding structures are the only textile constructs that are resistant to bending, shear, in-plane, and through-plane loads while they can tolerate torsion and internal pressure (Kamiya, Cheeseman, 2000).

Planar braided structures can be tailored in hierarchical organizations similar to the arrangement of natural tendons and ligaments. Moreover, they offer high tensile strength, which makes them suitable candidates for ligament tissue engineering. Laurencin *et al.* fabricated various braided structures from synthetic polymers such as PLGA and PLLA for generating artificial ligaments (Cooper et al., 2005, Cooper et al., 2007, Freeman et al., 2011, Freeman et al., 2009). The resultant scaffolds mimick the morphology and mechanical properties of native ligament. In a recent study, Freeman *et al.* twisted PLLA fibers together to form bundles, and in turn twisted three bundles together to form yarns that were braided at 69° to form a scaffold (Freeman, Woods, 2011). Polyethylene (glycol) diacrylate (PEGDA) hydrogel was embedded within the fabricated scaffold and the resultant composite was seeded with primary rabbit patella tendon fibroblasts. It was shown that PEGDA gel improved the cell proliferation and viability. Authors concluded that the mechanical properties of the braid-twist scaffold filled with 10% PEGDA were suitable for replacing anterior cruciate ligament.

Walters et *al.* twisted type I collagen fibers and then braided them to form a scaffold for ligament tissue engineering (Walters et al., 2012). They studied the effects of crosslinking with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and addition of gelatin on the cell activity and mechanical properties of the fabricated scaffolds. Primary fibroblast cells from the lateral and collateral ligaments of Sprague-Dawley rats were seeded on the braided scaffolds. The addition of gelatin significantly reduced the mechanical strength of the scaffolds while crosslinking with EDC improved the cellular activity during a 21 days period.

In another study, Fang *et al.* braided *pernyi* silk fibroin scaffolds and used them for tendon repair (Fang et al., 2009). The scaffolds were seeded with primary tenocytes and then implanted in adult New Zealand white rabbits and monitored over a 16-week period (Figure 7). The results showed that the implanted scaffold was successfully integrated with the adjacent tissues and formed a functional tendon. In a recent study, Barber *et al.* fabricated scaffolds using braided PLLA electrospun nanofibers for engineering tendons and ligaments (Barber et al., 2011). The tensile strength and Young's modulus of the fabricated scaffolds were in the range of 6.57 to 7.62 MPa and 47.6 to 55.0 MPa, respectively. These values are comparable with mechanical properties of a variety of native tendons and ligaments. For instance, the moduli and ultimate strength of human shoulder ligament are in the range of 5 to 42 MPa and 1 to 6 MPa, respectively. The results of *in vitro* studies indicated that human MSCs survived and covered the surface of braided scaffold over 21 days of culture. Similarly, Makridakis *et al.* showed that braided type I collagen fibers supported the attachment of muscle derived fibroblastic cells (Makridakis et al., 2009). Fan *et al.* used braided silk cords as scaffolds with high mechanical strength for growing MSCs in order to engineer anterior cruciate ligament in large animal models such as pigs. They showed that the implanted engineered ligaments met the mechanical requirements for daily activities (Fan et al., 2009).

In comparison to other textile structures, braided constructs offer the highest axial strength. The porosity and the mechanical properties can be adjusted spatially. Thus, in addition to connective tissues, braided structures might have the potential to be used for engineering tissues which require high in-plane mechanical strength.

3.4. Direct writing

Computer aided design (CAD) direct writing techniques have emerged as powerful tools for formation of scaffolds with high resolution and controlled pore size distribution (Moroni et al.). In direct writing, the fiber fabrication and scaffold preparation are performed as a single step procedure. This means that a continuous fiber is formed as it is written (printed) on a substrate creating a porous structure. Direct writing techniques are time consuming, but it is feasible to create complex 3D scaffolds by stacking multiple 2D layers for various tissue engineering applications such as bone (Kim et al., 2011, Landers, Pfister, 2002, Lee, Park, 2011b), cartilage (Neves, Moreira Teixeira, 2011), and heart tissue engineering (Berry et al., 2011, Gaetani et al., 2012). In addition, various materials including natural and synthetic polymers can be used for writing (Fedorovich, Moroni, 2010).

Berry *et al.* employed non-continuous direct writing to fabricate fibrous scaffolds from various biodegradable polymers including PLLA, PCL, and PLGA for supporting endothelial cells (Berry, Warren, 2011). The fabricated scaffolds were written as a web of connected fibers. Endothelial cells seeded on fibrous scaffolds were observed to proliferate both along the axis and around the circumference- of the fibers over a period of 6 weeks. The mass of all scaffolds was reduced due to hydrolysis. The L-PLA scaffold offered the lowest degradation rate among the studied materials. Kim et al. used direct writing and a repetition of writing and electrospinning to form PCL scaffolds for bone tissue engineering (Kim, Ahn, 2011). The scaffolds fabricated by direct writing method showed a higher mechanical strength compared to those produced by repetition of writing and elecrospinning. In another study, Ahn et al. used two techniques, direct writing and combined direct writing/electrohydrodynamic spinning, to generate PCL scaffolds for bone tissue engineering and to compare the physical properties of resultant scaffolds (Ahn et al., 2011). The results showed that the latter resulted in a more porous structure while the structures achieved by the former technique were stronger.

Direct writing systems are promising techniques as they allow precise control over the geometry and microstructure. They also allow fabrication of fibrous constructs comprised of different materials or combination of synthetic and natural polymers. Among the shortcomings of direct writing techniques are their slow fabrication rate and the fact that various stacked layers are not locked.

4. Fiber-based techniques for fabricating cell-laden constructs

Application of textile tissue engineering techniques has not been limited to the top-down approaches. Various bottom-up approaches have been developed to overcome the shortcomings associated with the top-down methods such as lack of control over cell distribution in the area or volume of scaffolds. The building blocks in the bottom-up techniques are cell-laden fibers and the assembling methods include random fiber deposition (Sugimoto et al., 2011), weaving (Onoe et al., 2011, Onoe et al., 2010), direct plotting (writing) (Cohen et al., 2006, Fedorovich et al., 2008, Fedorovich, Moroni, 2010, Gaetani, Doevendans, 2012, Ghorbanian, Qasaimeh, 2009), and winding (Liberski et al., 2011). Liberski et al. used a core-sheath setup where a core material with high mechanical strength was coated with cell-laden alginate (Liberski, Delaney, 2011). This configuration takes the advantage of the strength of the core to permit weaving or winding without the risk of fiber breakage. The reinforced fibers were used to encapsulate various cell types including human embryonic kidney (HEK-293) cells, human breast cancer (MCF-7) cells, human liver cancer (HepG2) cells, and mouse fibroblast (L929) cells. Cell-laden suture threads were then winded around a circular mandrel and formed a tubular structure mimicking a blood vessel.

In another study, Sugimoto et al. employed a microfluidic spinning system to form hybrid fibers with a mouse pancreatic beta cell (MIN6m9) encapsulated in a collagen core and an alginate sheath (Sugimoto, Heo, 2011). The fibers were deposited randomly and were implanted into the left kidney of three recipient diabetic mice and as a result their blood glucose concentration was decreased to normal level. Onoe *et al.* also employed a microfluidic system to fabricate fibers made of a core collagen-cell mixture and a calcium alginate sheath (Onoe, Gojo, 2011). They designed a micro-weaving machine to weave structures from cell encapsulated alginate-collagen fibers (Figure 8). They were able to produce simple structures; however, due to lack of mechanical stability, fabrication of complex geometries remained unfeasible.

Direct writing has the potential to form complex structures with a high resolution. Ghorbanian *et al.* designed an automated microfluidic direct writer (MFDW) which produced continuous cell-laden calcium alginate fibers (Ghorbanian, Qasaimeh, 2009). In this example, fibers were formed using two coaxial streams of sodium alginate containing cells in the middle and $CaCl_2$ as the gelling solution on the sheath. Layer-by-layer patterning of the fibers was controlled by moving a stage underneath the MFDW (Figure 9). The MFDW was employed for fabricating constructs made of various hydrogels containing different chemicals and cell lines. A challenge of this method is that fibers can slip on top of each other, which can reduce the mechanical strength of the engineered tissue in the in-plane direction.

5. Future opportunities

5.1. Fabrication of mechanically strong cell-laden fibers

The assembly of cell encapsulated fibers is a promising technique for building complex organs. Also, encapsulated cells can be protected from the patient's immune system. One of the main challenges in the use of cell encapsulated fibers is their low mechanical strength. As a result, it is both not possible to process them with conventional textile techniques and

the final structure is too fragile to be used. Thus, there is a need for finding reliable techniques to form strong fibers, which provide a suitable environment for cell growth. A recent attempt in this direction was to reinforce cell-laden hydrogels by using carbon nanotubes (CNTs) (Shin et al., 2012). It was shown that the mechanical properties of the CNT-gelatin methacrylate hybrid material could be regulated by altering the amount of CNT incorporated into the hydrogel system, making it suitable for various tissue engineering applications.

5.2. Forming a vasculature network in large tissues

The majority of existing tissue engineering methods relies on the diffusive transport of nutrients and oxygen into the tissue during the incubation period. This, however, limits the size of 3D organs that can be made. Indeed, a complex vascular network is required to deliver nutrients and oxygen to large organs. A variety of techniques have been explored to form biomimetic vasculature networks such as laser micromachining, soft lithography, electrostatic discharge, the use of hollow fibers, and sacrificial fibers (Huang et al., 2011, Takei et al., 2012). Esser-kahn *et al.* proposed a robust technique to embed a microvascular network in tissues (Esser-Kahn et al., 2011). They used a weaving machine to form a fibrous structure using a mixture of reinforcing and sacrificial fibers in a predesigned pattern. The sacrificial fibers were then thermally removed. In a recent study, Takei *et al.* embedded sacrificial poly(methyl methacrylate) PMMA fibers in agarose gel and removed them chemically to form a microvascular network of microchannels (Takei, Kishihara, 2012). Miller *et al.* wrote a sacrificial fibrous structure of carbohydrate glass, which was then covered with various cell-laden gels including agarose, alginate, PEG, fibrin, and matrigel (Miller et al., 2012). The sacrificial structure was dissolved in water and the formed microchannels were perfused with human umbilical vein endothelial cells (HUVECs). The fabricated micrvascular network significantly improved cell viability.

Although fiber-based techniques are promising for fabrication of interconnected vascular networks with similar architecture as native tissues, the removal process often requires harsh thermal or chemical conditions that prevent cellular encapsulation. The research path towards engineering of organs with an integrated vasculature network will likely require inventing and developing suitable sacrificial fibers and techniques that allow assembling them in 3D biomimetic designs.

5.3. FBTE for stem cell based therapy

FBTE have been used in combination with human stem cells for a variety of different biomedical applications. Electrospun nanofibrous scaffolds were combined with stem cells such as heart tissue formation, vascular tissue regeneration, bladder replacements, and cartilage repair (Hajiali et al., 2011, Pattison et al., 2005, Prakash et al., 2010, Zong et al., 2005). Fiber-reinforced hybrid scaffolds of PCL and slurries of homogenized cartilage-derived matrix were developed with biomimetic mechanical properties to promote adipose derived stem cell based chondrogenic differentiation (Kim et al., 2010, Kim and Im, 2008, Moutos et al., 2010, Moutos and Guilak, 2010b, Valonen, Moutos, 2010). In another study, PLGA scaffold systems impregnated with therapeutic transgenes were fabricated. The results of *in vivo* tests showed that the fabricated scaffold induced chondrogenic differentiation of adipose stem cells (Im and Kim, 2011, Im et al., 2011, Oh et al., 2011). Moreover, aligned neural stem cells on PLLA nano/microfibrous scaffolds have been shown to be effective for neural tissue engineering (Yang et al., 2005). An important finding is that the fiber topography and material plays a major role in regulating differentiation and proliferation of neural progenitor cells (Chaudhuri and Mooney, 2012, Christopherson et al., 2009, Trappmann et al., 2012).

Recently, combination of silk fibroin and stem cells are being increasingly used for fiber-based regeneration therapy and artificial tissue construct (Wang et al., 2006b). Wang *et al.* demonstrated that aligned electrospun silk fibroin nanofiber with 400nm diameter facilitated neuronal differentiation of human embryonic stem cells (Wang et al., 2012a). McCullen *et al.* developed nanocomposite scaffold by electrospinning PLA nanofibers containing multi-walled carbon nanotubes (MWNT), (Figure 10) (McCullen et al., 2007). MWNT loading of 0.25 wt% increased the tensile modulus of the electrospun nanofibrous mats. As shown in Figure 10c-d, adipose-derived mesenchymal stem cells proliferated and formed monolayer on the surfaces of the MWNT reinforced PLA scaffolds by day 1 and grew to confluency by day 14.

These research findings open new directions for the design of synthetic biomaterials which can be used for FBTE and other applications to regulate the cell responses. Further interdisciplinary investigations and utilization of FBTE technologies can open up wider biotherapeutic applications, particularly in the field of regenerative medicine.

6. Conclusions

FBTE hold great promise for creating functional engineered tissues. FBTE rests on a variety of fabrication techniques that can be used to make 3D constructs with a wide range of mechanical strength, porosity, and pore size distribution. The fibers, which are used as the building blocks, can be manufactured “on the fly” or in a separate process.

Among different fiber fabrication techniques, electrospinning has been widely used for fabricating tissue scaffolds owing to its relative simplicity and ease of control over the key process parameters. However, the encapsulation of cells is complicated, and the fabrication of large and complex 3D structures is not feasible using electrospinning. Wetspinning offers intrinsic higher porosity and larger pore size that make it more amenable to forming large 3D structures that allow for perfusion of solutions. Wetspinning is comparatively simple and can be used to form fibers from different materials, but long exposure to chemicals during the fabrication process can be harmful to cells. Microfluidic spinning is a promising approach for continuous fabrication of fibers with tunable morphological, structural, and chemical features. However, due to relatively slow fiber fabrication process, creating 3D structures is time consuming. Meltspinning facilitates the fabrication of fibers with irregular texture and cross-section, however, high temperature required during the fabrication process prevents encapsulation of cells within the fibers. Other techniques, such as interfacial complexation and biospinning have also been used which can be used for lab scale researches. In summary, each method offers a number of advantages while at the same time suffering from limitations, and which one to choose will depend on the application and intended use of the structures.

Fiber-based assembling techniques including knitting, weaving, braiding, and direct writing are mature technologies as they have been used in an array of engineering applications and can be tailored to meet the tissue engineering requirements. Knitting has become a popular method for various tissue engineering applications as 3D geometries with tunable mechanical properties can readily be produced. Weaving allows forming thicker constructs compared to knitted structures; however, the mechanical properties of woven structures are generally weaker. Braiding offer the highest axial strength among the fiber based techniques which makes it the preferred method for engineering connective tissues. Direct writing systems allow precise control over the geometry, microstructure, and cell distribution. Among the shortcomings of direct writing techniques are their slow fabrication rate and the fact that various stacked layers are not locked.

FBTE now comprises a palette of top-down and bottom-up methods that can be combined with new materials and applied to textile-based tissue engineering, stem cell therapy, vascularized tissues, and for organ replacement uses. Various forms of surgical meshes, wound patches, and engineered skin are currently being tested in clinical trials. Engineered ligaments have been implanted in pigs, presaging that more advanced scaffolds may soon be tested in humans as well.

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Highlights

We critically review the techniques used to form cell-free and cell-laden fibers and to assemble them into scaffolds. We compare their mechanical properties, morphological features and biological activity. We discuss current challenges and future opportunities of fiber-based tissue engineering for use in research and clinical practice.

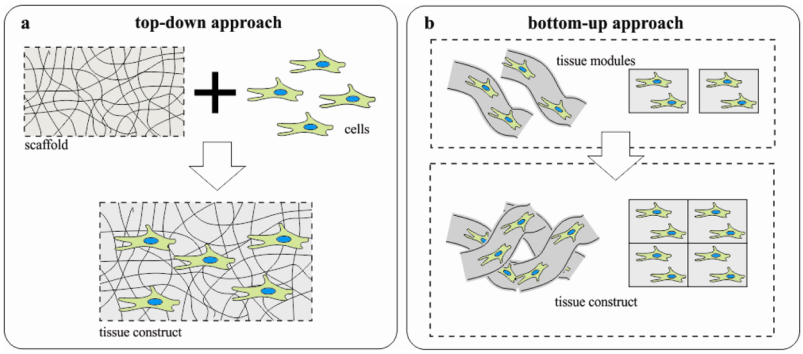

Figure 1.

Schematic diagrams of the top-down and bottom-up approaches for tissue engineering. (a) In the top-down approaches, cells are seeded on a porous scaffold and are incubated to proliferate and form a tissue; (b) In bottom-up approach cell-laden modules are assembled to form a tissue construct.

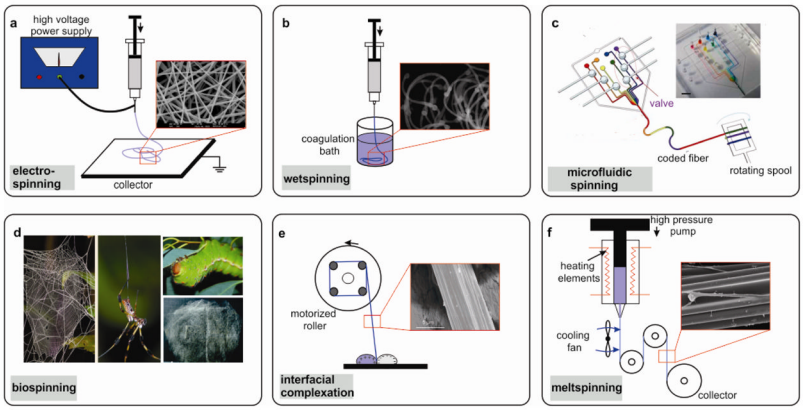

Figure 2.

Various techniques to fabricate fibers for tissue engineering applications. (a) In electrospinning, fibers are drawn by the flow of a viscoelastic polymer subjected to an applied electric field between an injecting needle and a collector plate in a distance from the needle; (b) Fibers in wetspinning are formed by injecting a polymer solution into a coagulation bath where they are cross-linked; (c) Microfluidic platforms produce fibers by coaxial flow of the pre-polymer and a cross-linking agent. They can be used for the production of functional cell-incorporating fibers. Image is adapted with permission from Macmillan Publishers Ltd: [Nature Materials], copyright (2011); (d) The process of fiber fabrication by various insects such as silkworm and spider is called biospinning; (e) Interfacial complexation technique includes the fabrication of fibers at the interface of two oppositely charged polyelectrolyte solutions by means of polyion complex (PIC) formation; (f) In the meltspinning process, a polymer is heated to its melting point and is extruded through a spinneret to form continuous fiber strands.

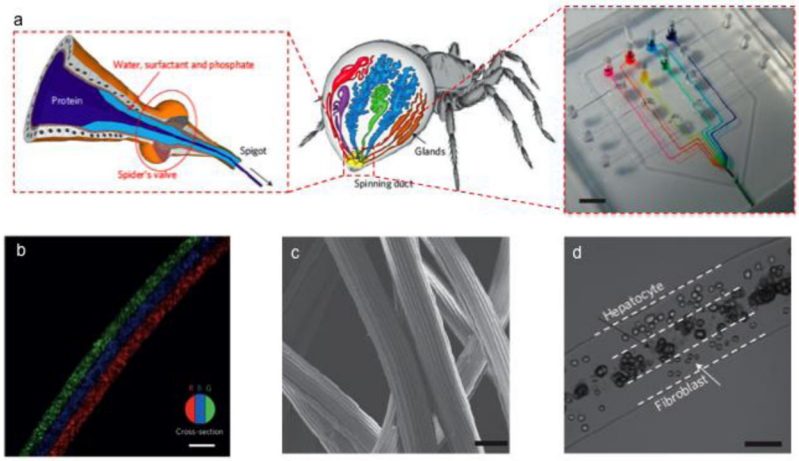

Figure 3.

Programmable physicochemical coding of microfibers. (a) A microfluidic chip inspired by silk-spinning system of spiders. The chip consisted of six controllable inlets for different alginate based chemicals and one inlet for $CaCl_2$ as the sheath fluid to generate a spinning process that mimics the spinning process of spiders. Pneumatic valves were used to modulate the composition of the fabricated fibers with millisecond response times. Fabricated fibers were collected by a motorized spool. (b) Parallel coding of alginate fibers; (c) Grooved fibres fabricated using the microfluidic chip with grooved round channels. The number and size of the grooves were controlled by changing the flow rate and shape of the channels; (d) Simultaneous delivery of hepatocytes and fibroblasts embedded in alginate followed by co-culture. Scale bares, 5 mm (a), 200 μm (b), 20 μm (c), and 100 μm (d) (Kang, Jeong, 2011). Images are adapted with permission from Macmillan Publishers Ltd: [Nature Materials], copyright (2011)

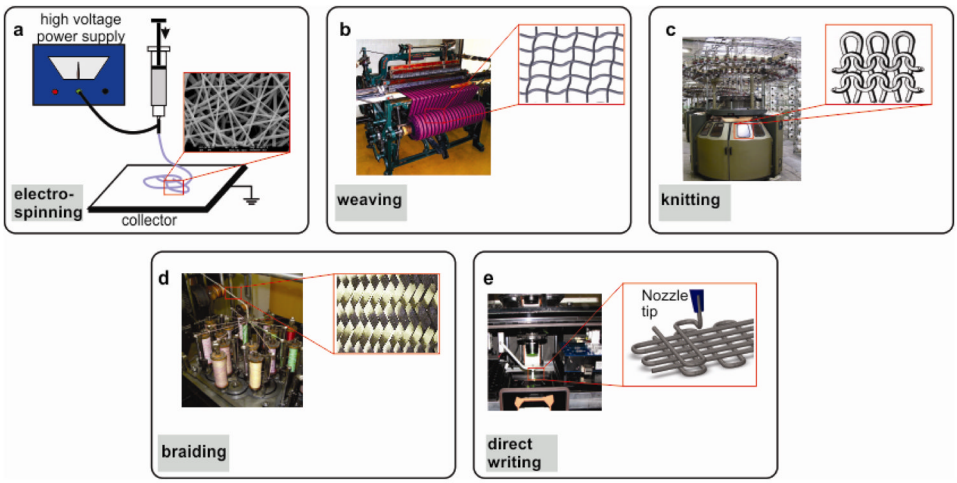

Figure 4.

Overview of the instruments and techniques used for fabricating fibrous structures and scaffolds and representative microstructures. (a) Electrospinning of polymeric fibers that are drawn under an applied electric field and deposited on a surface to form a fibrous scaffold; (b) Weaving of scaffolds by interlacing warp and weft fibers in perpendicular directions; (c) Knitting of yarns in a series of connected loops; (d) Braiding of fibers achieved by intertwining three or more fiber strands; (e) Direct writing of fibers by flowing or extruding fibers through a nozzle and simultaneously scanning across the substrate to deposit the fiber in a pre-designed shape.

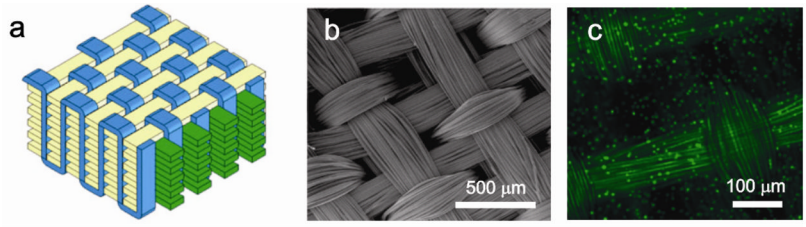

Figure 5.
PGA woven scaffolds. (a) Microstructure of a 3D orthogonally woven structure. 3D structures were woven by interlocking multiple layers of two perpendicularly oriented sets of in-plane fibers with a third set of fibers in the through-plane direction; (b) SEM image from the top surface of the construct; (c) Fluorescent image of a cell seeded construct illustrating uniform distribution of chondrocytes in fiber reinforced agarose (Moutos, Freed et al. 2007). Adapted with permission from Macmillan Publishers Ltd: [Nature Materials], copyright (2007).

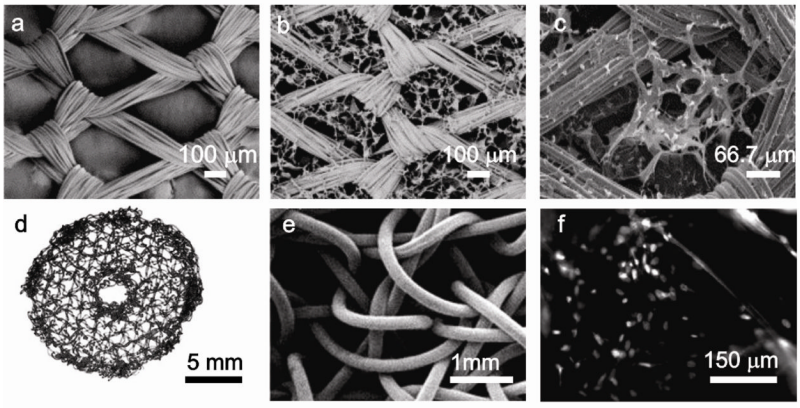

Figure 6.

Knitted and embroidered structures used in tissue engineering. SEM photomicrographs of: (a) PLGA knitted mesh; (b) PLGA–collagen hybrid mesh; (c) fibroblasts cultured in PLGA knitted mesh after five days incubation (Chen, Sato et al. 2005). Adapted with permission from Elsevier: [Journal of Biomechanics], copyright (2005); (d) A photograph illustrating the embroidered PCL scaffold for bone tissue engineering; (e) a SEM image of non-coated PCL fibers; (f) DAPI staining of collagen I coated PCL scaffold seeded with hMSC after 24 h cultivation (Rentsch, Hofmann et al. 2009). Adapted with permission from Springer: [Annals of Biomedical Engineering], copyright (2009).

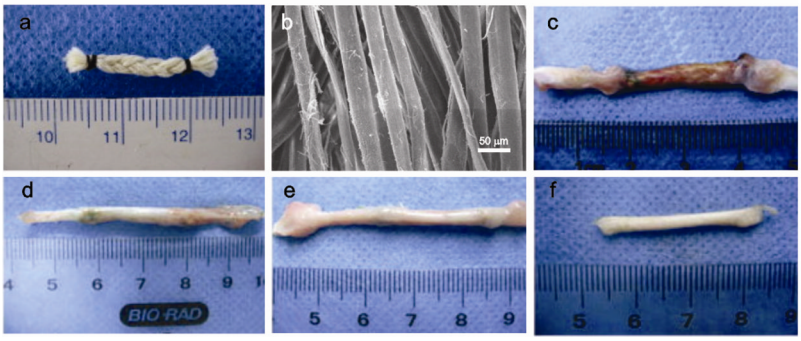

Figure 7.
Braided structure for tendon tissue engineering. (a) Braided silk scaffold; (b) SEM image of the A. pernyi silk scaffold; Regenerated tendon after (c) 6, (d) 12, and (e)16 weeks post-surgery; (f) a normal tendon of a New Zealand white rabbit (Fang, Chen et al. 2009). Adapted with permission from Elsevier: [Material Science and Engineering C], copyright (2009).

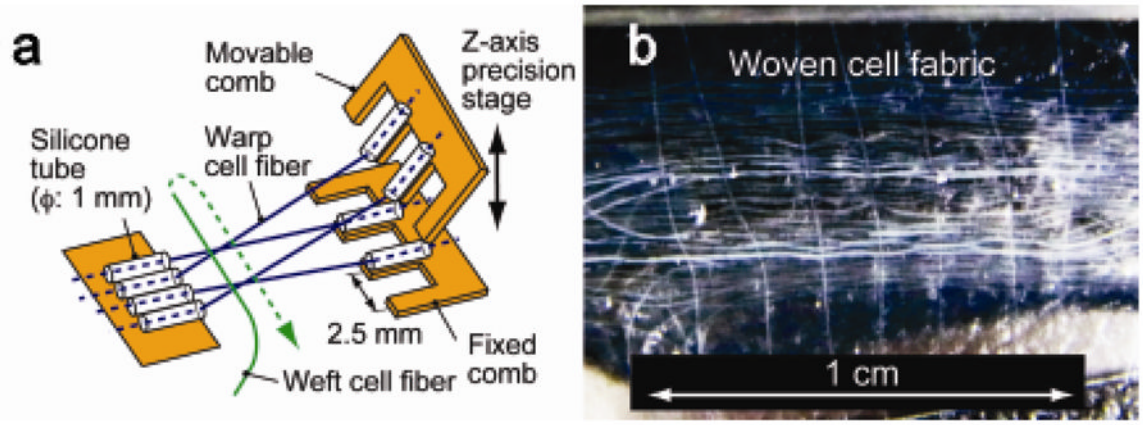

Figure 8.
Micro-weaving machine designed for weaving cell-laden alginate fibers. (a) Schematic of the setup; (b) image of a woven cell fabric formed by fibers made of a core collagen-cell mixture and a calcium alginate sheath (Onoe, Gojo et al. 2010).

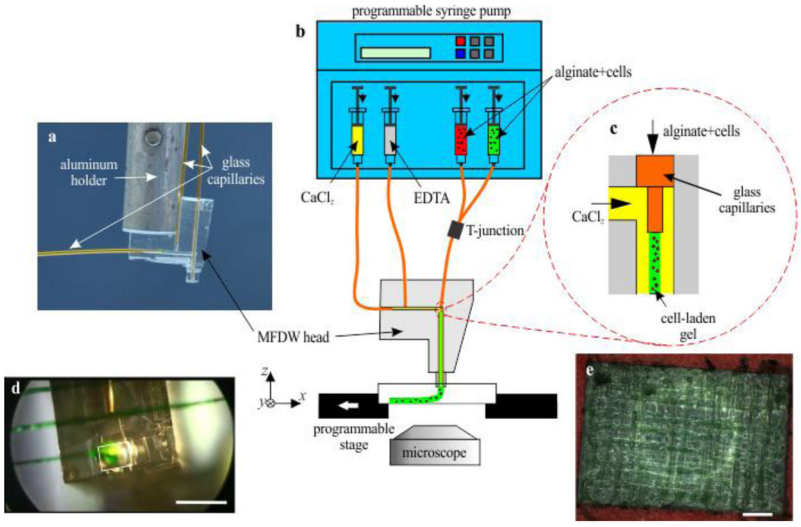

Figure 9.

Schematic of the MFDW system designed by Ghorbanian *et al.* (a) Image of a MFDW head made of PDMS clamped using an Al holder as well as capillaries that connect the MFDW to syringe pumps. The MFDW consists of three inlets for delivering cell suspended alginate, $CaCl_2$, and a declogging solution (EDTA), respectively. (b) Schematic of the setup, comprising the MFDW, a programmable stage, and an inverted fluorescent microscope for imaging. (c) A close-up view of the flow sheathing achieved by inserting a smaller, central capillary within a larger, outer capillary, which in turn is plugged into the PDMS microfluidic head. During the fiber formation process, $CaCl_2$ diffuses into the cell-laden alginate solution which gelates into fibers that are delivered through the MFDW head. (d) MFDW observed with the inverted microscope during the fiber writing. Green food dye was added to the alginate solution for visualization. (e) A slab of written fibers constituting a simple, porous 3D scaffold. Scale bars, 500 μm (d) and 1 mm (e) (Ghorbanian, Qasaimeh et al. 2009).

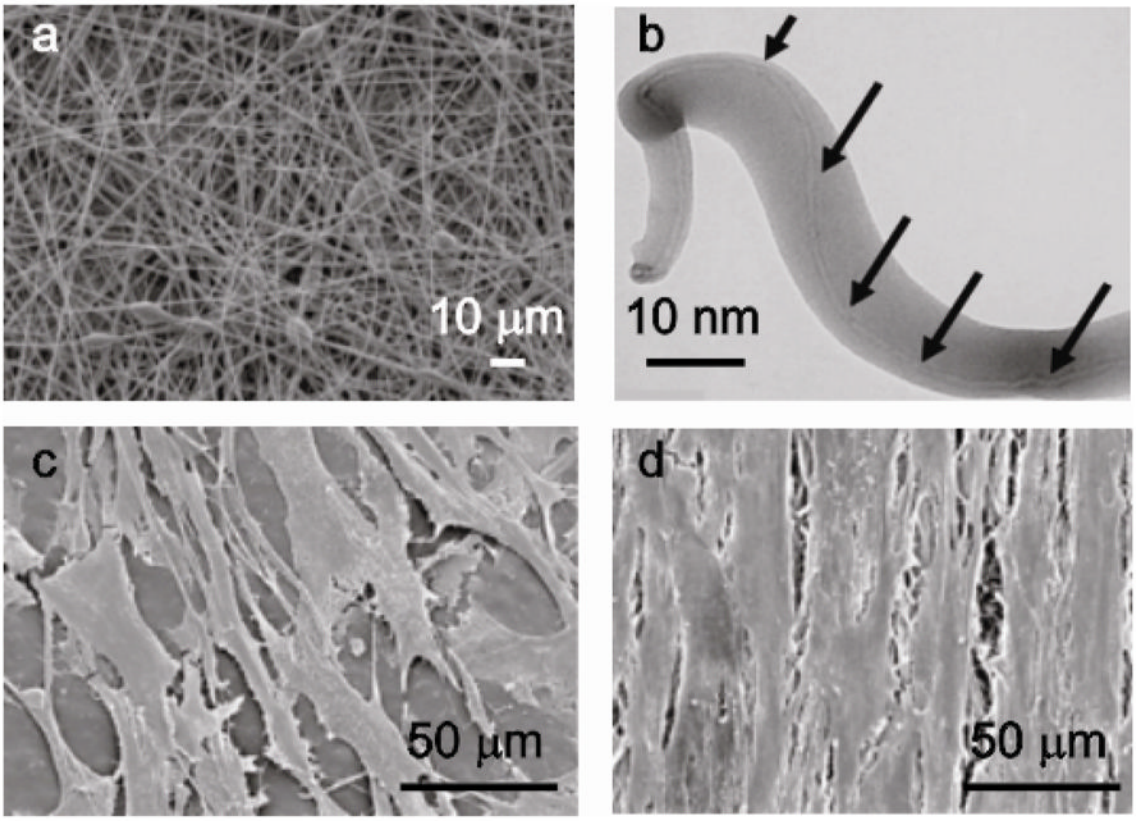

Figure 10.
SEM images of electrospun PLA nanofibers containing multi-walled carbon nanotubes. (a) fibers containing 1 wt% MWNT, (b) MWNT alignment along fiber axis; hMSCs grown on the surface of electrospun PLA with MWNT on (c) day 1 and (d) Day 14. (McCullen, Stevens et al. 2007). Adapted from Dovepress: [International Journal of Nanomedicine].

Table 1

A selection of existing tissue engineering studies which used scaffolds formed by fiber-based techniques.

Authors	Material	Physical and Mechanical properties	Targeted tissue (cell type)	Remarks
		Weaving		
Moutos *et al* (Moutos, Freed, 2007)	Polyglycolic acid (PGA) reinforced agarose and fibrin	Ultimate tensile stress: 67–85 MPa Young's modulus: 0.068–0.077 MPa	Articular cartilage (chondrocytes)	• A 3D weaving technique • The mechanical properties of the composite scaffold were comparable to native tissue • Composite scaffolds mimics the anisotropic, nonlinear, and viscoelastic biomechanical of cartilage • Use of reinforcement improved the aggregate and young's moduli by 4 and 15 folds, respectively
Moutos *et al* (Moutos and Guilak, 2008)	poly (ε-caprolactone) (PCL)	Ultimate tensile stress: 24 MPa Compressive modulus: 0.27 MPa	Articular cartilage	• PCL yarns of 150 μm diameters were woven similar to (Moutos, Freed, 2007) • PCL scaffolds were less stronger than PGA scaffolds in (Moutos, Freed, 2007)
Moutos *et al* (Moutos and Guilak, 2010b)	PCL supporting fibrin	Ultimate tensile stress: 22.9–35.3 MPa Young's modulus: 0.74 MPa	Articular cartilage (human adipose-derived stem cells)	• 1.4 mm thick scaffolds were formed by adopting a 3D weaving technique • Anisotropic properties in the in-plane direction
Volonen *et al* (Valonen et al., 2010)	PCL supporting fibrin	Aggregate modulus: 0.18–0.56 MPa Young's modulus: 0.05–0.4 MPa	Articular cartilage (human adipose-derived stem cells)	• Weaving properties of the scaffolds significantly affected the mechanical properties
Sahoo *et al* (Sahoo, Cho-Hong, 2007)	poly (D,L-lactide-co-glycolide) PLGA	Failure load: 97.2 N Elastic stiffness: 16.8 N/mm	Tendon and ligament (bone marrow stromal cells)	• Woven structures were stronger than knitted and hybrid scaffolds
		Knitting		
Sahoo *et al* (Sahoo, Cho-Hong, 2007)	PLGA knitted scaffold PLGA knitted scaffold coated with PCL PLGA knitted scaffold coated with PLGA nanofibers PLGA knitted scaffold coated with collagen	Failure load: 56.3–68.4 N Elastic stiffness: 4.3–9.1 N/mm	Tendon and ligament (bone marrow stromal cells)	• The stem cell-seeded rolled up scaffolds were 11% stronger than their unseeded counterparts after 3 weeks of culture • Cell proliferation and viability on the hybrid scaffolds increased during the third week • Viable cells were uniformly distributed on the seeded nanofibrous surfaces and also on the knitted silk microfibers in the depths of the hybrid scaffold

Authors	Material	Physical and Mechanical properties	Targeted tissue (cell type)	Remarks
				• Hybrid knitted scaffolds showed a lower stiffness while improved cell attachment
Ananta *et al* (Ananta, Aulin, 2008)	poly(lactic acid-co-caprolactone) (PLACL) supporting cell encapsulated collagen		Skin, bladder wall, and blood vessel (neonatal fibroblasts)	• Position of cells in the through-plane direction was controlled in the fabrication process
Chen *et al* (Chen, Sato, 2005)	PLGA knitted with collagen nanofibers		Skin (human foreskin fibroblasts)	• Hybrid scaffolds improved cell proliferation • *In vivo* experiments confirmed the formation of dermal tissues after 2 weeks • Dermal tissues became epithelialized within a month.
Gupta and Revagade (Guptaa and Revagade, 2009)	PLA wet spun fibers	Tensile strength: 0.03–0.33 MPa Porosity: 0.8–0.93	Urinary bladder	• The mechanical properties varies with the number of plies used in the yarn • The fabricated structures had higher mechanical properties than the targeted tissue
Chen *et al* (Chen et al., 2010)	Raw Bombyx mori silk supporting collagen sponge	Tensile strength: 6.72 MPa Stiffness: 28.26 N/mm	Tendon (human embryonic stem cells-derived mesenchymal stem cells)	• The mechanical properties of the engineering tendons were lower but comparable with the original tissue
Rentsch *et al* (Rentsch, Hofmann, 2009, Rentsch, Rentsch, 2010)	PCL embroidered structure covered with collagen or collagen and chondroitin sulfate (CS)	Porosity: 0.8 Pore size: 200–900 μm	Bone (human mesenchymal stem cells, ovine mesenchymal stem cells)	• In the presence of osteogenic supplements the hMSC showed an increasing Alkaline Phosphatase (ALP) activity up to day 14 and produced large amounts of calcified matrix after 28 days • Composite scaffolds enhanced cell proliferation and ALP activity. • Effectively induced the osteogenic differentiation
Ella *et al* (Ellä, Annala, 2011)	Poly(L/D)lactide 96/4	Porosity: 0.8–0.87 Tensile strength: 3.3–5.4MPa		• The mechanical properties were a function of number of ply in the yarn • The degradation rate of the knitted geometries was reported over a period of 52 weeks
Xu *et al* (Xu, Zhou, 2010)	Knitted polyester filament covered with polyurethane and N,N-Dimethyl formamide	Tensile strength (load): 92–145 MPa	Vascular graft	• Composite grafts showed a higher ultimate strength and strain that the knitted structure
Dai e*t al* (Dai, Kawazoe, 2010)	PLGA knitted mesh combined with collagen microsponge	Young's modulus: 7.24 MPa–14.62 MPa Stiffness: 50.5–55.2 N/mm	Articular cartilage (bovine chondrocytes)	• Three PLGA/collagen hybrid scaffolds of different structural design," thin", "semi", and "sandwich" were prepared in this study

Authors	Material	Physical and Mechanical properties	Targeted tissue (cell type)	Remarks
				• Semi and sandwich offered a better mechanical properties • The mechanical properties were lower but comparable with bovine articular cartilage
Sahoo *et al* (Sahoo, Lok Toh, 2010)	Degummed knitted native silk fibroin coated with PLGA electrospun nanofibers	Scaffold ultimate strength (load): 95.6 N Composite scaffold: 61.5–75.3 N	Ligament and tendon (bone marrow derived stem cell)	• The stem cell-seeded rolled up scaffolds were 11% stronger than their unseeded counterparts after 3 weeks of culture • Cell proliferation and viability on the hybrid scaffolds increased during the third week • Viable cells were uniformly distributed on the seeded nanofibrous surfaces and also on the knitted silk microfibers
Liu *et al* (Liu et al., 2008)	Raw Bombyx mori silk fibers knitted fibers combined with silk sponge	Pore diameter of knitted structure: 1mm Tensile strength (load): 250 N Tensile stiffness: 40 N/mm	Anterior cruciate ligament (human bone marrow-derived mesenchymal stem cells)	• Composite scaffolds improved cell attachment and proliferation • Composite scaffolds had similar mechanical properties with the knitted structure but they maintain their mechanical properties over a 2 week period
Wang *et al* (Wang, Li, 2012b)	PLGA knitted structure supporting collagen-chitosan hydrogel	Surface area: 2.01 after 1 week-2.74 after 4 week Tensile strength: 3.6 MPa	Skin	• Implantation in rats indicated angiogenesis start from early stages of implantation • Angiogenesis rate was faster in the hybrid scaffold in comparison with pure knitted PLGA construct
		Braiding		
Cooper *et al* (Cooper, Lu, 2005, Cooper, Sahota, 2007)	PLGA and PLLA fibers	Tensile strength (load): 332 N reduced to 92.8 N in 12 weeks Young's modulus: 354.4 MPa reduced to 53.8 N in 12 weeks	Anterior cruciate ligament (rabbit and mouse anterior cruciate ligament fibroblasts)	• Increasing braiding angle increases surface pore area • Braids composed of the same number and type of yarns differ in strength due to differences in strain rate and geometry • The mechanical properties of the seeded structure degraded over time (Cooper, Sahota, 2007) • The stress–strain curve was similar to the values for natural ligament tissue • The 3-D circular fibrous scaffold could withstand the tensile load applied on native ligament • 100–300 μm pore diameters showed best results

Authors	Material	Physical and Mechanical properties	Targeted tissue (cell type)	Remarks
				• *In vivo* performance of the developed cell- seeded, tissue-engineered ligament construct demonstrated excellent healing and regeneration potential
Walters *et al* (Walters, Kwansa, 2012)	Collagen fiber crosslinked with and without gelating using either UV or 1-ethyl-3- (3-dimethylaminopropyl) carbodiimide (EDC)	Tensile strength: 1.07–19.3 MPa Young's modulus: 6.32–148 MPa Tensile strain: 18–20%	Anterior cruciate ligament (primary mouse anterior cruciate ligament fibroblasts)	• The mechanical properties of EDC crosslinked collagen fiber braid twist scaffolds without gelatin are similar to native anterior cruciate ligament • Adding gelatin lowered the mechanical properties
Fang *et al* (Fang, Chen, 2009)	Antheraea pernyi silk fibroin	Tensile strength (load): 50 N after 12 weeks implantation 16 N after 12 weeks implantation	Tendon (tenocytes)	• Enhanced adhesion and propagation of the tenocytes on the scaffold • *In vivo* data confirm efficient neo-tendon formation • Bundles of collagen fibers in the neo-tendons were uniform and well oriented
Barber *et al* (Barber, Handorf, 2011)	Poly (L-lactic acid) (PLLA)	Tensile strength: 6.57–7.62 MPa Young's modulus: 47.6–55.0 MPa	Tendon and ligament (human mesenchymal stem cells)	• The mechanical properties of the braided scaffold depended on the number of bundles involved in the construct • 3 bundle scaffold had a higher mechanical strength than the 4 and 5 bundle scaffolds
			Direct writing	
Kim *et al* (Kim, Ahn, 2011)	Melt plotting of PCL fibers followed by electrohydrodynamic deposition of a layer of PCL fibers	Porosity: 0.5–0.68 Tensile strength: 1.7–4.1 MPa Young's modulus: 14.6–41.3 MPa	Bone (osteoblast-like cells (MG63))	• Hybrid scaffold displayed higher viability and calcium deposition compared with the normally fabricated scaffold • Hybrid scaffolds had a lower mechanical strength in comparison with the pure melt-plotted PCL scaffold
Lee *et al* (Lee, Park, 2011b)	α-tricalcium phosphate- based cement mixed with alginate	Porosity: 13.3–53.7 Young's modulus: 96–573 MPa	Mesenchymal stem cells (MSCs)	• Scaffolds with three different porosity were fabricated • The scaffolds with the highest porosity resulted in the best cell proliferation • Upon implantation of a sample in a rat calvarium with a critical size defect the defect region was fixed • Biological proteins can be loaded on the scaffolds to be released in-vivo over a time period

Authors	Material	Physical and Mechanical properties	Targeted tissue (cell type)	Remarks
Berry *et al* (Berry, Warren, 2011)	Poly(L-lactide), Poly(D,L-lactide), Poly (DL-lactideecoeglycolide), and PCL		Microvascular network (Human umbilical vein endothelial cells)	• Scaffolds formed by biodegradable suspended branched fibers were formed • Endothelial cells adhered to the surface all the fabricated scaffolds • Cultured cells proliferated on fibrous scaffolds proliferate both along the axis and around the circumference of the fibers • Cells cultured on non-suspended fibers did not follow the pattern and attached to the substrate
Anh *et al* (Ahn, Lee, 2011)	PCL written by either rapid prototyping or electro hydrodynamic (EHD) writing	pore size: 205–347 μm Porosity: 0.56–0.78 Young's modulus: 6.3–12.5 MPa	Bone (osteoblast-like cells (MG63))	• Electro hydrodynamic writing method is achievable in a lower pressure and temperature in comparison with rapid prototyping • EHD written structures indicated a better cell proliferation, alkaline phosphatise activity, and calcium mineralization over 14 days of cell culture