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Medical Textiles as Substrates for Tissue Engineering

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Abstract

Tissue engineering (TE) and regenerative medicine, with the aim to replace, repair and remodel the damaged tissues and organs, has led to development of myriad biomimetic materials that possess biomechanical properties resembling those of native tissues. Some of the key points to generate a successful replacement for native tissues are selecting the appropriate cell types and incorporating them into biomimetic three-dimensional (3D) scaffolds or substrates. Different types of biomaterials, including degradable or nondegradable materials with various morphologies and structures, can be used as scaffolds to provide a hospitable and supporting environment for cell growth and tissue regeneration. Fibrous scaffolds have been extensively used in regenerative medicine applications. Specifically, biomedical textiles with fibrous structure have a long history in treatment, repair, and replacement of tissues. While some applications are as simple as bandages

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or sutures, others are more complex like repair of heart valves, vascular grafts, and engineered skeletal muscle tissue. The fibrous structures/textiles can be developed in a way that their shapes and sizes match the tissue's or organ's structure or mechanics while enabling cellular infiltration due to their highly porous structure. In this chapter, we briefly discuss the fibrous structure applications in TE and regenerative medicine. Then, we review the background of medical textiles and summarize the fabrication methods for fibers and fibrous scaffolds with different morphologies and structures used in various TE applications (e.g. musculoskeletal, eye, cardiac, and nerve tissues). At the end, we highlight the future of medical textiles in regenerative medicine applications.

***Keywords*:** Medical textiles, tissue engineering, fibrous scaffolds biodegradable polymers 3D scaffolds.

11.1 Introduction

11.1.1 Concept of TE

Tissue engineering includes the isolation and culture of specific cell types onto 3D scaffolds with tissue-inducing supplements (such as growth factors) to generate tissues similar to the native ones and transplant the engineered tissue into the patient [1, 2]. As human body has a limited ability to regenerate the defects and injuries (e.g. cardiac muscle infarction), regenerative approaches, including TE, are being developed with the aim to regenerate, remodel, replace, or treat injured tissues and organs. Moreover, they can also help in starting the regeneration process by activating the body's self-healing capability [2]. There are three approaches in TE research: *in vitro*, *in vivo* and *in situ*. The engineered constructs can be developed *in vitro* and then transplanted as a functional tissue replacement in the body. In the second approach (*in vivo* TE), following the *in vitro* development of the constructs, the scaffolds with cells are transferred to the body and reconstruction of functional tissue occurs inside the body. In the case of *in situ* TE, the substrates with the ability to release the biomolecules or growth factors are transferred to the body to attract the host stem cells or tissue-specific progenitor cells by physicochemical and biological cues [3].

Fabrication of scaffolds with suitable architectures and mechanics is as important as cell type selection in the development of engineered tissues. When designing functional constructs, the following fundamental requirements must be considered: (i) proper cell-biomaterial interactions such as cell adhesion and promoting extracellular matrix (ECM) deposition, (ii) degradation at a controllable rate that is comparable with the rate of tissue regeneration itself, (iii) sufficient transport of gases, nutrients, and

other biomolecules to allow cell survival, proliferation, and differentiation, and (iv) biocompatibility (i.e., low degree of inflammation or cytotoxicity *in vivo*) [3, 4]. Different biomaterials from bioceramics to biopolymers have been used in order to generate 3D scaffolds. Some synthetic and natural polymers such as polyurethane (PU) [5–7], poly-L-lactide (PLA) [8, 9], poly (ethylene glycol) (PEG) [10, 11], alginate [12, 13], and chitosan [14, 15] have been used while natural polymers usually have weaker mechanical properties compared to other synthetic materials [16]. In some studies, ECM components [2, 17–19] have also been employed as natural biomaterials for TE applications. The ECM is composed of fiber-forming proteins such as collagen, elastin, keratin, laminin, fibronectin and vitronectin, as well as non-fiber-forming proteins like proteoglycans, glycosaminoglycans (GAGs) and soluble factors (soluble proteins in the network that are essential for cells function and are helpful for cells signaling) [20–22]. The ECM is a heterogeneous network where its composition varies between native tissues where specific cells in each organ are responsible for constantly rebuilding its structure [21]. Tissues such as tendon, ligament, and bone have high levels of organized fibers to withstand the mechanical forces that the tissues experience in the physiological condition. While some soft tissues comprise much higher levels of unorganized fibers such as skin, others like cardiac and skeletal muscle tissues are mainly composed of organized fibers. Therefore, in every tissue, the arrangement and composition of ECM fibers can generate fine-tuned mechanical properties [2, 23]. In TE process, "polymer nanofibers" and nanofibrous scaffolds play the same critical role to mimic the native ECM structure and mechanics and subsequently guide the cell growth [24]. Therefore, in this chapter, we will review the concept of TE and the importance of fibrous structures in regenerative medicine. Then, we will discuss the background of medical textiles and highlight the methods developed to fabricate fibers and fibrous scaffolds for various TE applications. In particular, we will discuss the use of biotextiles in musculoskeletal, eye, heart valve, and nerve TE. This chapter is aimed to provide an overview of the past, present and future of medical textiles and fibrous structures for TE applications.

11.1.2 Background of Medical Textiles in TE

The term "biotextile" refers to the class of fibrous textiles that are being used in biological environment, including human body. In the past, biomaterials were defined as inert materials, which are stable without any changes in mechanical or chemical properties when in contact with the tissue. However, nowadays this definition has been totally revised. Biomaterials

should interact actively with cells, immune system and biological fluids while guiding and improving the tissue's growth and functionality. In addition to being non-toxic, if bioresorbable, they should be degraded to non-toxic by-products and replaced by the newly created ECM/ tissues [25].

Patients who need transplantation of tissues always face severe shortage of viable and compatible organs. However, after transplantation, they are still dependent on the lifelong immunosuppressive medication to reduce the risk of rejection. Due to the shortage of self or donor tissues for transplantation of various tissues, other strategies have been explored to allow development of grafts that can restore the disrupted function of the injured tissue. Tissue engineering has emerged as a promising platform that allows engineering tissue-like constructs with biomimetic and similar biological function as the target tissue. To achieve this aim, a biocompatible scaffold that can interact with human cells and surrounding tissues and induce regeneration and restoration of the function is critical. Thus, a significant portion of the activities in the field of TE has been dedicated to engineering biomimetic scaffolds [26].

Due to the similarity of the medical textiles based fibrous scaffolds to the ECM structure, these constructs are attracting noticeable attention for the TE applications. Researchers in the field of polymer science, textile, and fiber technologies have attempted to develop different fabrication methods and to synthetize materials for soft tissues TE. Depending on the type of the damaged tissues, various kinds of fibers with different surface morphologies, diameter sizes and porosities have been developed to provide suitable topography, microstructure, mechanical properties, leak resistance, degradation rate, electrical conductivity, and cell compatibility to regulate cell proliferation, growth, migration, and differentiation [26]. Figure 11.1 shows briefly different aspects of scaffolds developed as target cell niche [27].

The medical textiles refer to the category of textiles that are used in medical procedures. They can either be used as implant or simply can be used as a bandage interfaced with human body. Similarly to other medical materials, the performance of medical textiles depends on bio- and immune-compatibility of the constructs with cells, immune system and biological fluids [27]. The oldest applications of medical textiles include sutures for closing wounds and bandages for covering wounds and damaged tissues. In both cases, the fibers and fabrics have been used to provide mechanical support and holding the damaged tissues until natural closure and regeneration. However, the suturing threads have evolved in the past few years and now they can be used for delivery of cells, biological factors, and even sensing modalities to the injury site to modulate the environment, prevent infection, induce healing, and measure the regeneration

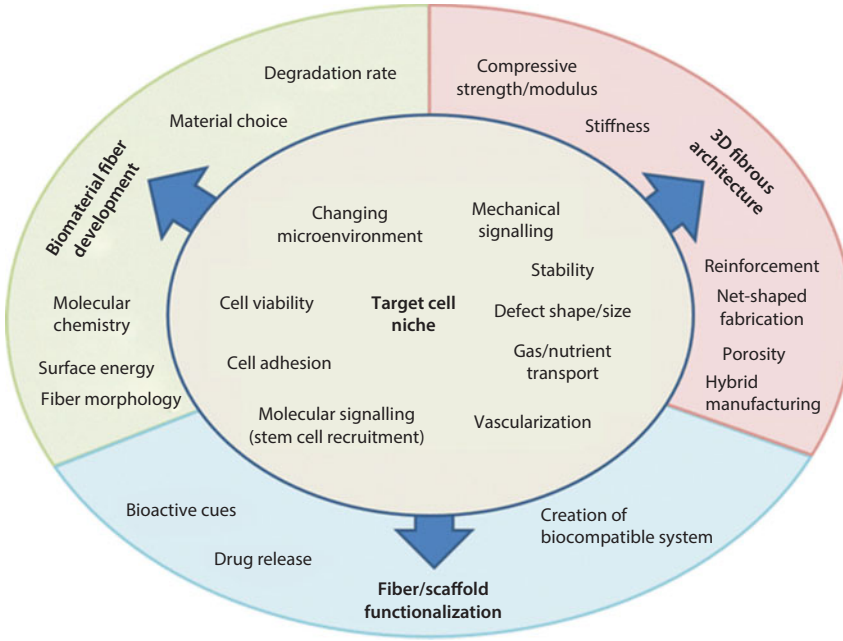

Figure 11.1 Scaffold requirements for an appropriate cell target niche. An appropriate template for cell niche should replicate its structural architecture and provide optimal conditions for transporting gas, nutrient and biomolecules as well as growing tissue. Adopted with permission [27]. Copyright 2016, Springer.

rate. For example, application of natural silk fibers as sutures for wound closure has been known for centuries and recently Gulrajani *et al.* [28] showed that the integration of a silver coating on silk fibroin fibers revealed an antimicrobial property, making it suitable for sutures. Later on along with the advancement of surgical procedures, meshes and fabrics were used as surgical meshes to fix the damage to internal tissues such as hernia repair. These meshes still do not offer biological activity and rely on natural regeneration for healing by providing adequate mechanical support. The widespread use of these medical textiles is owing to the possibility of tailoring the mechanical properties and mimicking the anisotropic properties of native tissues [27]. Currently some of the commercial biomedical textile products, available in the market, are TIGR Matrix (to reconstruct the breast tissue after cancer or as an abdominal wall closure) developed by Novus Scientific, Uppsala, Sweden; ULTRAPRO *ADVANCED*™ (inguinal and ventral hernia repair), produced by Ethicon US, LLC, USA; and INTERGARD SILVER™ (as woven/knitted vascular grafts) created by Maquet GETINGE Group in Rastatt, Germany [29].

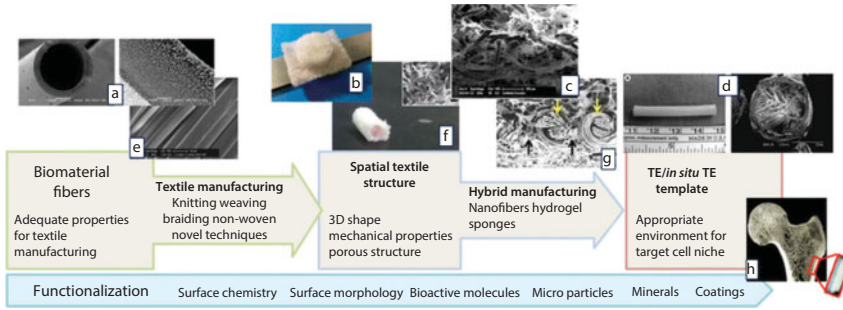

Figure 11.2 Development of fibrous scaffolds and textile structures for TE. Adopted with permission (a) [30] Copyright 2011, Elsevier, (f) [31] Copyright 2010, Elsevier, (g) [32] Copyright 2013, Elsevier, other images [27] Copyright 2016, Springer.

Recently, the advancements in biomaterial development and TE have called for creating scaffolds that can mimic the physical characteristics of native tissues and cellular growth. Thus, due to versatility of the various textile processes, biotextiles have been a promising option for producing TE scaffolds. Figure 11.2 briefly shows the engineering process of biomaterial fibers and textile manufacturing techniques and types of fibrous scaffolds used in TE. In the next section, we review some of the fiber-based fabrication methods applied to develop fibrous scaffolds.

11.2 Fiber Formation Approaches

11.2.1 Wet Spinning

Wet spinning is a traditional technique to develop polymer-based fibers. In this technique, a polymer-based solution is run through a syringe using a syringe pump into a coagulation or cross-linking solution to form continuous fibers [29]. The coagulation or cross-linking solution is comprised of a non-solvent and/or a poor solvent depending on the polymer characteristics [33]. Using this technique, fibrous scaffolds with relatively large pore size (~250–500 μm) and fairly thick fibers (30–600 μm) with various morphologies could be fabricated [34]. The fiber's diameter could be varied by varying the flow rate of solution or needle size [29]. Wet spinning technique could be applied for the development of fibers from a wide range of polymers, including natural polymers such as alginate [35, 36], collagen [37, 38], chitosan [39–41], silk [42, 43] and gelatin [44] and synthetic polymers such as poly-ε-caprolactone (PCL) [45] and PEG [46]. This technique is more useful when

the cross-linking process of prepolymer solution is fast. For instance, alginate with rapid cross-linking process by calcium chloride ($CaCl_2$) is the most applied polymer in wet spinning process. Since the prepolymer solutions as well as the coagulation bath are often compatible with cells, this technique could be applied to encapsulate live cells and provide 3D scaffold for cells [47, 48]. For instance, Arumuganathar and Jayasinghe [48] developed cell-laden multi-compositional fibrous structures using a three-needle pressure-assisted spinning approach in which living cells were spread in the inner layer.

11.2.2 Melt Spinning

Another technique is melt spinning process which is based on heating the polymeric resin above its melting temperature (T_m) and extruding it using a spinneret in the air to be solidified. While the process temperature is higher than T_m, it should be lower than the decomposition temperature of polymer. After the polymer is solidified, while the temperature is between the glass transition temperature (Tg) and the T_m of polymeric resin, the fibers undergo a sequential stretching, leading to sequential thinning of the fibers [49]. Polymers derived from lactide, glycolide and caprolactone monomers have been widely studied in melt spinning process [50–52]. For instance, poly (L-Lactic acid) (PLLA) fibers were fabricated by a two-step melt spinning process in order to develop 3D braided fabrics for TE [52]. In another study, fibers of starch: PCL as well as starch: PLLA with volume ratio of 30:70 were fabricated using melt spinning process for bone TE application [53]. The results demonstrated the ability of these scaffolds to prompt cell adhesion and proliferation to regenerate bone defects [53]. Similar study was performed on a blend of poly(3-hydroxybutyrate) (P3HB) and PCL to develop hollow fibers from a wide range of PHB/PCL compositions using melt spinning with improved elastic properties compared to pure PHB fibers [54].

11.2.3 Microfluidic Spinning

Microfluidic technology in combination with electrospinning is another approach to fabricate fibers with different shapes and sizes, like core/sheath and hollow fibers, without using complicated tools. Advantages of microfluidic devices to fabricate fibers include the ability to spin multiple fibers in parallel through multichannel arrays, rapid prototyping, and easy fabrication process [55, 56].

In a microfluidic system with multi-flow channels, phase separation that enables to form the coaxial flow and consequently fibers can be formed by cross-linking the core flow. The core flow can be cross-linked via chemical

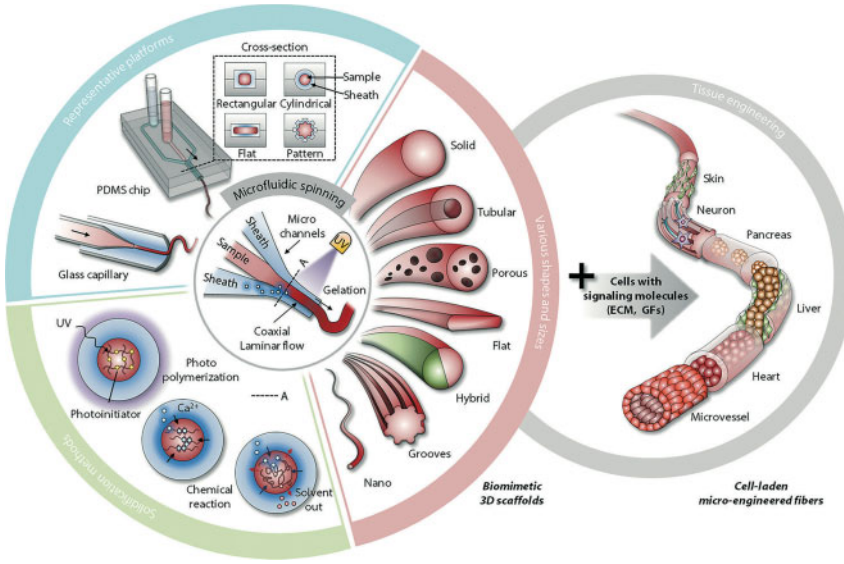

Figure 11.3 Overview of the fibers fabrication with different morphologies using microfluidic spinning technique for TE applications. The fibers with different patterns can be cross-linked by UV or chemically. To fabricate cell-laden fibers, cells can also be incorporated into the fibers to model a specific organ or tissue. Adopted with permission [55]. Copyright 2014, the Royal Society of Chemistry.

or photo (e.g UV light) polymerization (Figure 11.3) [55]. Jeong *et al.* [57] developed 4-Hydroxybutyl Acrylate (4-HBA) tubular fibers by using 364 nm UV light for cross-linking the polymer. To fabricate the alginate fibers with different morphologies (e.g. coded fibers with various chemical compositions and topographies along the fibres, and metre-long core/shell fibers), a specific microfluidic system was used due to the fast cross-linking of sodium alginate using chemical reaction of $CaCl_2$ solution [58, 59]. This method enabled to fabricate cells-encapsulated microfluidic-based fibers of alginate or blend of alginate and gelatin methacryloyl (GelMA) which revealed viability of cells up to 3 days of culture [47]. Shi *et al.* [60] also presented a fabrication method to develop microgrooved GelMA fibers by microfluidic technique which could induce skeletal muscle cells alignment on the surface of the fibers resembling myofibrils structure. Microfluidic system is also a well-known approach to fabricate core/sheath and several hollow fibers structures. For example, two-layer microchannels were designed to flow poly (vinylpyrrolidone) (PVP) solution as sheath material and heavy mineral oil or pyrrole + PVP as the core phase through an array of spinners. The diameters of the fibers fabricated by using this system were about 100–250 nm [61].

11.2.4 Self-Assembly

Self-assembly is a process of molecular arrangement and organization into patterns or structures involving non-covalent forces such as hydrogen bonding, hydrophobic forces and electrostatic interactions [23]. Self-assembly of natural or synthetic macromolecules results in nanoscale supramolecular structures, or even nanofibers (originally fabricated by electrospinning) with diameters 5–25 nm, which is considerably thinner than fibers. However, this low efficient method has shown to require more complicated procedures [23, 62]. Liu *et al.* [63] reported self-assembly of polyphenylene dendrimers into micrometer-long nanofibers. Using various solvents such as chloroform ($CHCl_3$), tetrahydrofuran (THF) and their mixtures with water, the study showed that the self-assembly of fibrous layer could be obtained on a hydrophobic surface. They observed that the morphology of the dendrimer nanofibers highly depends on pH value, substrate's contact angle, type of solvent, and preparation method. The self-assembly process was also applied to encapsulate the cells within the nanofibrous structure of peptide amphiphiles (PAs), derived from a collagen ligand. After injection in an animal body, a self-assembled nanofibrous network was developed. Results revealed that self-assembled peptide nanofibers disordered by sonication process could simultaneously assemble into a nanofibrous scaffold reversibly even after multiple cycles of destruction and refabrication [63–65].

The techniques that have been discussed in this section can be used to fabricate fibrous scaffolds with different properties and architectures depending on the specific applications. Different designs (e.g., woven/non-woven, braided, knitted, and bioprinted) provide specific structural and mechanical properties for the scaffolds, which are appropriate for tissue regeneration or replacement. These properties including cell/scaffold interaction and cell morphologies can be optimized and controlled for a given application. In the next section, we will briefly explain some of the fiber-based architectures used for TE.

11.3 Fiber-Based Architectures for the TE Scaffold

11.3.1 Woven Fabrics

Weaving, in which two distinct sets of yarns (wefts and warps) are interlaced perpendicularly to form fabrics, has been widely used for creating clothing for a long time [66, 67]. Woven structures can be generated in different patterns (Figure 11.4a), which can affect the flexibility and physical

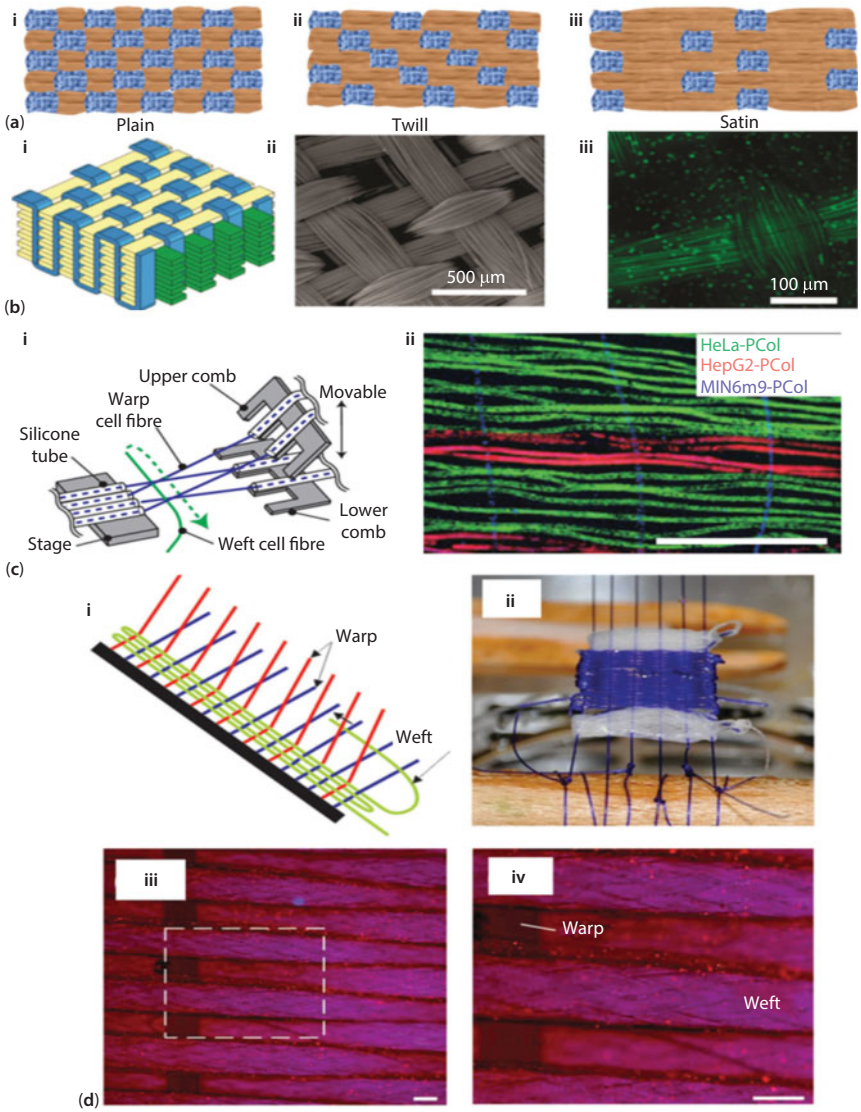

Figure 11.4 Application of woven fabrics in TE. (a) Different common weaves including plain (i), twill (ii), and satin (iii). (b) 3D woven construct fabricated by interlocking several layers for cartilage TE, schematic (i), SEM image of woven PGA scaffold (ii), the same PGA scaffold covered with condrocyte-laden agarose (iii) [77] Copyright 2007, Nature Publishing Group. (c) Process of weaving hydrogel fabrics using a microweaving loom (i), a patterned hydrogel fabric (ii) [58, 59]. Copyright 2013, Nature Publishing Group. (d) Assembly of composite living fibers using an off-the-shelf weaving loom (i, ii), micrographs represent a fabricated cell-laden fabric (iii, iv) [47] Copyright 2014, Wiley-VCH. Reproduced with permission [29]. Copyright 2016, John Wiley and Sons.

characteristics of the fabric. Other important factors that affect the flexibility as well as the porosity of the generated fabric are the numbers of warps and wefts per square inch and the size of the fibers and threads used in fabrication [68]. The weaving process can be tuned and scaled up easily; therefore, woven fabrics have been applied in areas such as composite fabrication and biomedical engineering. Comparing with knitted or braided constructs, woven structures are more flexible, but can only endure less force in the through-plane direction [29]. Woven fabrics are also less porous compared to knitted structures and possess smaller pores inhibiting cell penetration and tissue ingrowth. Therefore, it would be less applicable for load-bearing tissues where the scaffolds mechanical properties are substantially affected by fibers structure and arrangement. In load-bearing applications, the through-plane mechanical properties can be improved by interlocking multiple layers of woven fabrics and fabricating thick 3D structures [69].

Woven fabrics are widely used in TE as scaffolds or as reinforcement mats in hydrogels to improve the mechanical properties of the structure. In a pioneering study, Moutos *et al.* [70] used a 3D weaving approach to create poly (glycolic acid) (PGA) yarns into fabrics in which various layers of the fabric were interlocked to enhance the through-plane load-bearing properties. In this study, chondrocyte-laden agarose gel was reinforced with woven fabric of PGA for cartilage TE (Figure 11.4b). Other groups have also fabricated reinforcing structures from different materials such as silk, PCL, and polypropylene using similar approaches [71–76]. Recently, few efforts have been made to assemble cell-laden fibers to create woven fabrics with tunable mechanical properties and to control the cellular distribution. In this case, hydrogel fibers were used as cell carriers and then assembled as part of the fabrics (Figure 11.4c) [58]. To overcome the challenge of low mechanical properties of the hydrogel fibers and to facilitate the assembly process, composite fibers with a load-bearing core polymer and cell-laden hydrogel in shell have been fabricated [47]. These fibers could be assembled using regular weaving looms (Figure 11.4d).

11.3.2 Knitted Fabrics

Knitting is another textile process in which fibers and threads are interlaced in a defined arrangement of connected loops (Figure 11.5a,b) [78]. The properties of the knitted fabrics can be tailored by adjusting the types of stitches and the yarn material. Knitted fabrics have also been used for various biomedical applications such as medical gauzes and surgical meshes

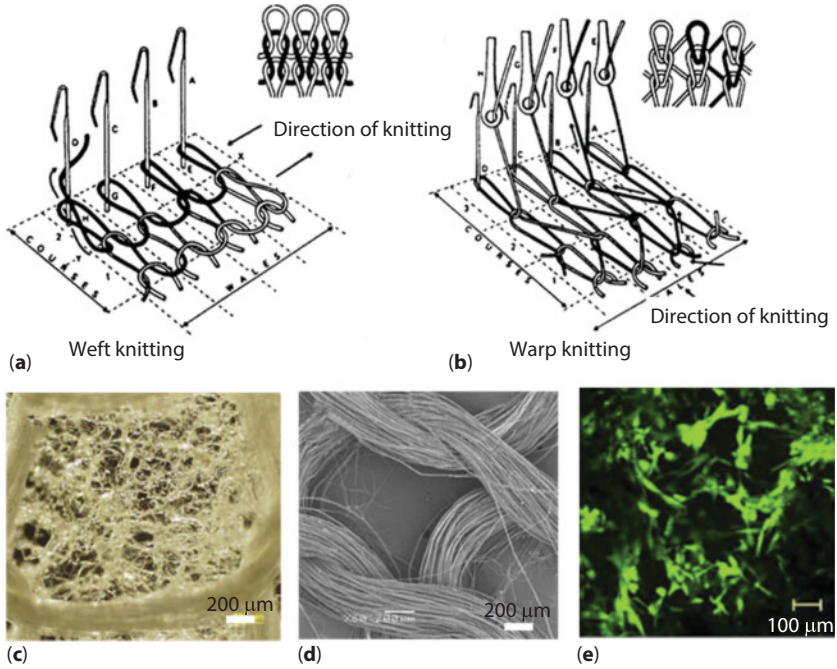

Figure 11.5 (a,b) Schematics representing various knitting processes and stitches; (a) weft and (b) warp knitting. (c) Knitted silk scaffold coated with collagen. (d) Knitted silk scaffold. (e) hMSCs grown on the hybrid structure of knitted scaffold and collagen coating [78] Copyright 2000, Elsevier. Copyright 2008, Elsevier. Adopted with permission [29]. Copyright 2016, John Wiley and Sons.

[29]. The fabrication process is very attractive for use as TE scaffolds due to the variability of the fabric and robustness of the knitted scaffolds fabrication process [79–83]. For example, knitted silk-collagen sponge scaffold has been seeded with different types of cells such as human embryonic stem cells (hESCs) and human mesenchymal stem cells (hMSCs) for tendon and ligament regeneration, respectively (Figure 11.5c–e).

Due to excessive mechanical stresses that fibers experience during the assembly process, knitting of cell-laden hydrogel fibers has been a major challenge. However, recently, the development of cell-laden composite fibers has enabled their assembly into 3D knitted fabrics by developing new knitting machines equipped with computer aided design (CAD) systems which have resulted in 3D constructs with defined microstructure [29]. However, fabrication of multicellular patterns with tunable properties in different directions has still remained a challenge [29].

11.3.3 Braided Fabrics

Braiding is a textile process consisting of more than three fibers or threads intertwined. Braided constructs offer high axial and radial load-bearing properties in comparison to the other textile constructs [84–87]. Braided constructs are usually fabricated in circular or tubular shapes with dense walls; thus, these scaffolds have been used as sutures, stents, nerve regeneration conduits, and for other TE applications in the past [88–90]. The type of material and size of the fibers control the structural and mechanical characteristics of braided constructs [85]. However, high density of the fibers and small pores of the constructs are the challenges to overcome for efficient cell penetration through the braided fabrics. To address these issues and eliminate the need for cell infiltration, cell-laden fibers have been braided into scaffolds during the process resulting in 3D constructs integrated with living cells [29]. Owing to their architecture, flexibility and dimensional stability, braided conduits have also been used as nerve conduits [91]. In a well-known study, a multilayer braided PLA-based conduit was fabricated to regenerate a 10 mm length of nerve gap in the rat sciatic nerve. After 8 weeks of implantation the scaffold was well integrated and surrounded by the neighboring tissue. In contrast, engineering of non-cylindrical architectures using braiding is a challenge, which limits their applicability to only irregularly shaped tissues.

11.3.4 Non-Woven Fabrics

Fibrous structures can also be engineered by stacking fibers without interlocking or interlacing them. In this case, fibers can be physically entangled or can be sintered using a binder. Common methods of fabrication of non-woven fabrics include electrospinning, blow spinning, air-jet spinning [92], and dry spinning [93].

The term "electrospinning" derived from "electrostatic spinning" has been used since 1930 [62]. In the regenerative medicine applications, electrospinning, with ability to easily set up and scale up the fabrication process, is an appealing technique to fabricate 3D fibrous constructs with high volume to surface area and interconnect porosity [62]. The four major components in standard electrospinning system (Figure 11.6) are (i) an electrically conductive spinneret, (ii) a syringe pump, (iii) a grounded collector, and (iv) a high-voltage power supply. The fiber formation from polymer solution is by overcoming the electrostatic force due to the surface tension of the charged droplet at the spinneret tip, which generates a liquid jet. Due to the electrostatic interactions between surface charges of droplet and the

Coulombic force applied by the electrical field, the liquid drop elongates by whipping continuously and deposits on the grounded collector. Finally, a non-woven fibrous membrane forms on the grounded collector after the solvent has evaporated [94]. Changing the collector type from a simple plate to a rotating drum provides different scaffold architectures by transforming random fibers into aligned fibers in the scaffold's structure. When a disc or a cylinder rotates at a high speed, fibers are collected along the direction of rotation [24, 95]. Heat treatment of the fibers can also produce porous fibers or hollow rods (Figure 11.6). In some studies, two parallel

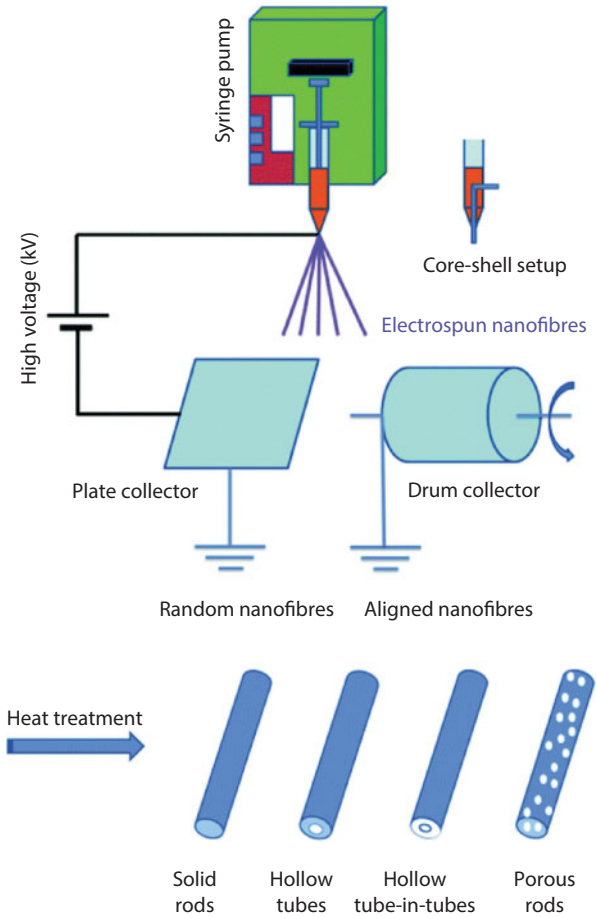

Figure 11.6 Schematic illustration of electrospinning process with different types of collectors to fabricate random or aligned oriented fibers. Further heat treatment process can change the morphology of the fibers from simple solid to hollow or porous tubes. Adapted with permission [95]. Copyright 2016, the Royal Society of Chemistry.

plates connected to the ground were used to collect the aligned fibers in the small distance between the two plates [96–98].

The morphology of fibers depends on various factors such as viscosity and electrical conductivity of the polymer solution, molecular weight of the polymer, applied voltage, distance between the needle and the collector, size of the needle and flow rate, as well as environmental parameters such as temperature and humidity [99, 100]. In general, increasing the concentration of solute, and consequently the solvent viscosity, results in larger fiber diameter and higher porosity in the fabricated scaffold. Moreover, higher electrical conductivity of the solution reduces the fiber diameter, while the higher spray rate increases the fiber diameter [100]. Chemical and physical properties of the fibers such as crystallinity, hydrophilicity and degradation rate can be tuned by surface modification and incorporation of biomolecules. Figure 11.7 shows the different concepts and methods to modify fibers or immobilize biomolecules on them. An overview of some TE applications with these fabricated electrospun fibers obtained from natural and synthetic polymers is also presented in Table 11.1.

In blow spinning, dry spinning and jet spinning, similar to electrospinning, the polymer is dissolved in a volatile solvent and a high electrical field or high-speed air jet breaks the polymeric solution stream into smaller streams and pushes them towards a collector plate [109]. Non-woven fabrics are the most popular form of textiles used in biomedical applications, partly due to their ease of fabrication, scalability, the ability to tune the mechanical and structural properties of the scaffolds while resembling the microarchitecture of ECM in human tissues.

Non-woven fabrics provide higher surface area than most of the other medical textiles. The porous structure also enables cellular ingrowth while the material integrity allows for customized performance and controlled degradation profile [110]. Although controlled pore size can facilitate cell infiltration, creating patterns in the structure that allow incorporation of cells into the filaments of the fabric has remained a major challenge. This is due to the toxic solvent or high voltage that compromises the cell survival during the fabrication process. Recently these scaffolds have been used as a substrate for flexible electronics and wearable devices such as temperature sensors or strain gauges [111].

11.3.5 Bioprinting

2D or 3D printing is a computer-controlled technique to fabricate scaffolds and is a new approach in addressing traditional TE issues such as the lack of ability to control fibers architecture and arrangement in a scaffold

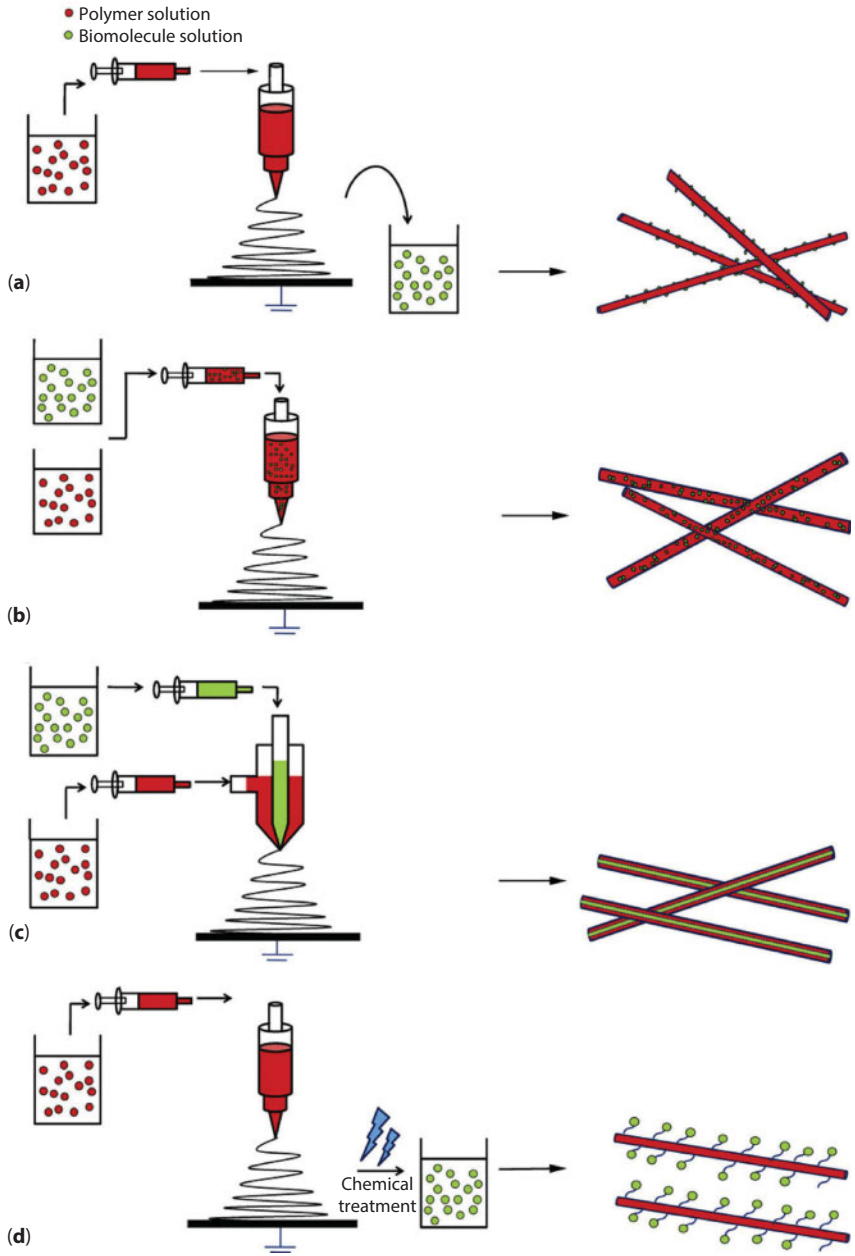

Figure 11.7 Schematics of different methods to load biomolecules in electrospun fibers. (a) Adsorption of biomolecules on the surface by post processing. (b) Loading the initial polymeric electrospinning solution by biomolecules. (c) Co-axial spinning with shell and core from different biomaterials and core containing biomolecules. (d) Chemical treatment of fibers to immobilize the biomolecules. Adopted with permission [101]. Copyright 2014, the Elsevier.

Table 11.1 Overview of some of the electrospun fibers from natural and synthetic polymers and their biomedical applications.

Polymer	Application	Ref.
PCL	Nerve tissue	[102]
Collagen	Wound healing	[103]
Gelatin	Skeletal muscle	[104]
PCL/gelatin	Cartilage	[105]
Poly (glycerol sebacate) (PGS)/gelatin	Cardiovascular	[97]
PGS/PCL	Cardiovascular and cornea	[96, 98]
Silk fibroin	Tendon	[106]
Poly (lactic-co-glycolic acid) (PLGA)	Nerve tissue	[107]
PLLA	Kidney	[108]

[112–116]. Although bioprinting is similar to printing process in some technical aspects, cells and biomolecules, like growth factors or other functional elements could be integrated in the polymer during the process leading to 3D constructs with cells distributed throughout the scaffold [2, 117]. 3D bioprinting can be divided into three main categories including (i) laser-based [118] (ii) inkjet-based [119], and (iii) extrusion-based bioprinting techniques (Figure 11.8) [120, 121]. As shown in Figure a mixture of cells, biomaterials such as hydrogel and biomolecules can be prepared as printable inks and transferred into the nozzle for printing. Hydrogels such as collagen, gelatin, Matrigel (commercial product from gelatinous protein mixture), agarose, and alginate act as bio-inks in this process and are printed in different patterns based on the desired architectures for the cell-encapsulated scaffolds. Lastly, the bioprinted constructs were incubated for a specific period of tissue culture [122, 123].

Among the three techniques, extrusion-based bioprinting has been used in a recent study to fabricate fibrous scaffolds [124]. Extrusion-based bioprinting system consists of cells mixed with ink (usually hydrogel) filled in a micro-nozzle that is connected to the syringe pump to extrude the material and fabricate 2D or 3D constructs. In this technique, the pressure level or the displacement of the pump piston control the fiber structure and arrangement [125]. A 3D network structure can be formed by stacking 2D patterns via layer-by-layer approach. Following printing each 2D layer, the ink material can be solidified or cross-linked physically or

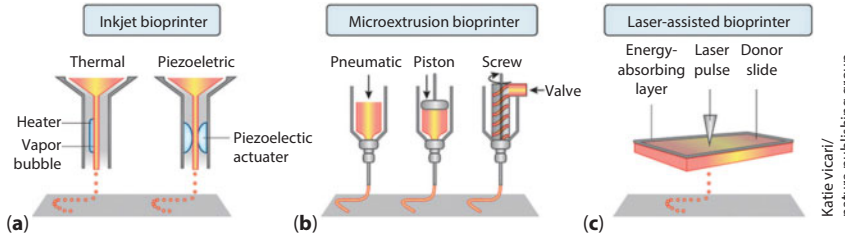

Figure 11.8 Three different approaches in bioprinting to fabricate a scaffold: (a) Inkjet bioprinter to electrically produce air pressure to force the droplets to form a fiber. (b) Microextrusion bioprinter to extrude the material, like mixture of hydrogel and cells, into fiber. (c) Laser-assisted bioprinter, using laser to force the mixture of cells and hydrogel to be collected on the collector. Adapted with permission [116]. Copyright 2014, Nature Publishing Group.

chemically prior to fabricating the next layer [122]. 3D fibrous construct of osteoprogenitor cells mixed with hydrogel (alginate) was developed using the bioplotter approach. The viability of printed cells was studied for different working parameters such as printing time, hydrogel type, and needle diameter. The findings indicated that the bone marrow stromal cells mixed with alginate survived during the printing while maintained their functionality and eventually differentiated to the osteoblast lineage [122]. In the next section, we will explore the applications of biotextiles for TE and regenerative medicine.

11.4 Applications of Medical Textiles in TE

11.4.1 Musculoskeletal Tissues

Musculoskeletal diseases caused by various traumas, infections, inflammation, or genetic disorders disturb the functionality of load-bearing tissues [126, 127]. Various treatments are available consisting of tissue grafts (autografts, allografts, or xenografts) and replacement of the impaired tissue with artificial prostheses [128]. Despite the promising results, there are some issues including injury to donor site, post-surgery infection, and limited availability of graft materials which limit the tissue's durability and functionality [129]. To overcome these limitations, and improve the clinical outcome, TE could be a potential alternative approach enabling the creation of functional tissues for organ replacement.

One of the critical steps in the successful engineering of load-bearing tissues is designing biodegradable scaffolds that can withstand the

mechanical forces experienced by the tissues in the physiological environment. For example, having suitable properties to initiate the bone regeneration or affording physical support for the fracture of the spine are the necessary requirements in bone TE. Textile technologies have been widely applied to create constructs with distinctive characteristics to provide the desired physical and mechanical properties for regeneration of load-bearing tissues. By using appropriate materials and textile fabrication techniques, fibers and fiber-based 3D porous scaffolds have been developed to obtain properties similar to the native tissues [130–132]. The main benefit of textile constructs for load-bearing tissues is their flexibility and elasticity, which are obtained by control over the design [133]. Moreover, vascularization of the engineered tissues could be controlled via varying the porosity and pore sizes to obtain the desired porosity for TE applications. For instance, knitted constructs with large pore sizes have shown a great potential to support vascularization and tissue ingrowth [84].

Among the textile fabrication techniques discussed above, electrospinning is a well-recognized and powerful approach to provide micro and nanofeatures in applications for load-bearing tissues such as bone and cartilage [133, 134]. The constructs to be created for the regeneration of mineralized tissue such as bone and dentin need to be bioactive to develop chemical bonding with host tissue. According to Hench and Paschall [135] study in 1973 on the concept of chemical bonding of bioactive materials, controlled release of Ca, P, and Na ions from the surface of the bioactive materials results in an alkaline pH and the body can incorporate the ions into newly formed tissues. In order to prevent acute inflammation in this application, the chemical bonding is the important factor to be considered [136]. To achieve this proper chemical bonding, various kinds of bioactive materials such as bioactive glass [135, 137, 138], calcium phosphate based ceramics [139, 140] and forsterite [141–144] have been used alone or as fillers in the fabrication of composite fabrics. Electrospun fibrous scaffold's surface also was modified previously using bioactive coatings to control tissue integrity and to achieve suitable interaction with host tissue. In some studies, hydroxyapatite (HA) was biomimetically deposited on the surface of fibrous scaffolds when they were immersed in supersaturated solutions such as simulated body fluid (SBF) [145, 146]. Araujo *et al.* [147] modified the surfaces of PCL fibrous scaffolds using dilute sodium hydroxide solution. In the next step, fibrous scaffolds were immersed in a solution containing calcium and phosphate ions to deposit biomimetic HA layer. In another study, non-woven fibrous cell-free PGA scaffold was soaked in hyaluronic acid and allogeneic serum of blood to attract the chondrocyte cells, initiate the matrix protein production and stimulate the regeneration of intervertebral disc in rabbits [148].

The exceptional mechanical properties of bone tissue are determined by HA nanocrystals incorporated between aligned collagen fibers and the composite structure of bone [149]. Therefore, in addition to the surface bioactivity, the mechanical property of scaffolds is another important factor to be considered in the fabrication process after implantation, and the scaffold should be able to support physical loads that the tissue experiences or be able to transform these loads through the injured bone to enhance bone regeneration. This requirement is still a challenge in the fabrication of electrospun fibrous scaffolds and researchers are looking for approaches to overcome this issue. For instance, Kharaziha *et al.* [143] incorporated forsterite nanopowder within PCL fibrous scaffolds and revealed significantly enhanced mechanical properties compared to pure PCL scaffold. They claimed that forsterite nanopowder itself with better mechanical properties than other bioactive ceramics such as HA and bioglass resulted in a promising construct for bone TE. In another study, Deng *et al.* [149] applied novel load-bearing fibrous scaffolds using electrospinning and polymer blending techniques for bone regeneration. After fabrication of electrospun PLGA/ poly ((glycine ethyl glycinate)$_1$ (phenyl phenoxy)$_1$ phosphazene) (PPHOS) blend, they were rolled up in a concentric way to duplicate the bone laminated construct. They demonstrated that the highly porous scaffold (~87%) possessed tensile strength comparable to that of the trabecular bone [149].

One of the most important properties of electrospinning process is the ability to incorporate various kinds of drugs and growth factors necessary for bone regeneration [150, 151]. As shown in Figure 11.7, therapeutic drugs and growth factors could be either directly incorporated within polymer matrix or be encapsulated in a core of core-shell double layered constructs for release in a controlled manner, during the regeneration of bone tissue [142, 150, 152]. In a recent study, 15% (w/v) dexamethasone was loaded in PCL-forsterite nanocomposite fibrous scaffolds during solution preparation. Results demonstrated a successful differentiation of stem cells from human exfoliated deciduous teeth (SHED) to bone specific cells after 28 days of culture in normal medium [144].

Non-woven constructs fabricated by electrospinning process have been used for cartilage TE with promising results for translational study [153–157]. For instance, Erggelet *et al.* [157] investigated the effect of hyaluronic acid coating on the non-woven PGA scaffold used for cartilage TE. In an *in vivo* study they showed that a cartilaginous cell-rich tissue formed following implantation of this scaffold in the articulate cartilage defects of merino sheep [157]. Electrospun fibrous scaffolds have also been widely designed for use for osteochondral applications [158, 159]. For example,

Zhang and Mo [159] developed a bilayer fibrous scaffold of collagen and PLA to study the effect of this bilayer scaffold on the osteochondral regeneration via seeding MSCs and implanting them in a rabbit osteochondral defect model. Yunos *et al.* [158] also developed bilayer fabrics of electrospun poly-D-L-Lactide (PDLLA) fibrous layer and bioglass for osteochondral tissue. They showed that chondrocyte cells could attach, proliferate and migrate into the fibrous fabrics. Yokoya *et al.* [160] studied the tendon-bone insertion regeneration, using a non-woven PGA sheet, for the restoration of rotator cuff defects in rabbits. After the regeneration, the injured part revealed a well-arranged fibrocartilage layer mostly restored using type III collagen. In another study, non-woven chitin fibrous scaffold was implanted into a defect site of the infraspinatus tendon [161]. The scaffolds promoted collagen fiber alignment in the regenerated tissue and provided a better substrate for cell attachment compared with untreated defects. However, the mechanical properties of the scaffold were not appropriate for this application and in the early postoperative period, the detachment of some materials from the bony trough was observed. Moreover, some of the specimens also failed at the tendon-bone insertion [161]. Despite the promising results reported in those studies, the electrospun scaffolds used in those studies were extremely thin and the mechanical properties of these constructs were not adequate to tolerate the applied loads on the large defect sites of those tissues. To overcome these issues, other textile fabrication technologies alone or in combination with electrospinning technique have been developed [47]. Knitted technique has been extensively applied to engineer and repair damaged bone tissues [47, 79–81, 83, 162]. It could be due to higher mechanical properties and larger pore sizes of the knitted fabrics compared with the electrospun sheets. The pore sizes are large enough (~100μm) to allow cell infiltration and tissue ingrowth [47]. For instance, the regeneration of metacarpophalangeal joints in rheumatoid arthritis patients was studied using a knitted PLLD scaffold [163]. Following 2 years implantation, no implant fracture or intramedullary osteolysis were reported which were the benefits of the knitted constructs compared to silicone implant used as control in the study [163]. They also followed up the patients with implants after 7 years and found that while a considerable pain relief was reported but the scaffolds functionality was impaired [164]. In another study, Shen *et al.* [31] developed knitted constructs of silk and collagen in which cell homing factor SDF-1 alpha was incorporated to regenerate Achilles tendon. Results confirmed that enhanced local endogenous SDF-1 alpha and ECM production was obtained after 4 weeks of implantation [165]. In another study, hybrid scaffolds comprised of knitted silk fibers and silk sponge were developed and used as ligament grafts.

Similarly, HA was coated on the scaffolds to improve osteoconductivity and osteointegration with host bone for "bone–ligament–bone" graft. The osteoinductivity of HA-coated scaffolds improved the osteogenic differentiation of bone marrow MSCs [82].

Woven fabrics are normally stiffer and stronger than knitted ones, providing an improved ability to preserve stability of constructs under mechanical loading [166]. In a study, Shikinami *et al.* [167] fabricated lumbar and cervical 3D woven discs consisting of tri-axial fiber alignment to improve the physical weaknesses of biological intervertebral discs. Furthermore, HA was deposited on the surface of the discs to stimulate new bone formation. Based on the results and evaluation of long-term *in vitro* durability of the scaffolds and animal tests, the 3D discs can be promising for clinical use in human disc replacement arthroplasty [167]. In another study, woven collagen scaffolds with densely compacted and anisotropically aligned constructs were developed to topographically stimulate tenogenesis [168]. This scaffold could serve as a substrate to reconstruct functional ligaments and tendons. Layered woven PLLA fabric was also fabricated with two different surface morphologies in the inner and outer surfaces to treat defects in the infraspinatus tendon [169]. While the outside of the construct showed a smooth surface, a rough surface covered the inside. After implantation, a large amount of cell migration was observed on the rough surface compared to the smooth surface, and after 8 weeks of implantation, the strength of intact infraspinatus tendon was recovered. Derwin *et al.* [170] clinically utilized woven PLA scaffold to augment the rotator cuff defects in dogs. They showed that while the stiffness of the scaffolds did not change considerably, ultimate load was significantly enhanced compared with the un-augmented restoration (23%). 3D weaving techniques have also presented potential for generating specially defined geometries, making it suitable for TE [70, 75, 171–173]. This technique is also applied when high mechanical properties are required for scaffolds in applications like tendon regeneration. Moutos and coworkers [70, 75, 174, 175] employed composite 3D woven scaffolds of PCL for the engineering of biomimetic functional cartilage tissue. They put the PCL woven fabrics in a tough hydrogel such as mixture of alginate and polyacrylamide to build a functional scaffold that mimics the load-bearing and tribological properties of native tissue [75].

Braiding technique provides 2D and 3D rope-like fabrics with either dense, hollow, or with embedded core structure [87, 176]. These complex braided constructs are distinguished from knitted or woven fabrics by their flexibility in axial and radial load-bearing directions, superior abrasion and fatigue resistance specifically during bending, torsion and traction [86, 87].

The high mechanical properties of braided fabrics as well as fiber alignment in the scaffolds have made them excellent candidates for engineering articular and connective tissues that experience high loading and contain aligned ECM fiber to provide the required strength (e.g, cartilage, tendon, and ligament) [177]. Anterior cruciate ligament (ACL) is the most commonly injured intra-articular ligament of the knee. A major challenge in ACL-TE is the regeneration of articular cartilage with construct that presents anisotropic and heterogeneous mechanical properties. Braiding technique with ability to control braiding direction, fiber alignment and density, and number of layers has been shown to be a suitable technique to develop ACL grafts with biomimetic characteristics [88, 90, 178]. Various kinds of synthetic materials such as poly (lactic acid co-ε-caprolactone) (PLCL) [89] and PLLA [178] or composite fibers of synthetic and natural materials such as 50% type I collagen and 50% poly (vinyl alcohol) (PVA) [88] have been used in the past for ACL TE. Synthetic biomaterials provide the necessary mechanical strength while natural biomaterials provide a suitable microenvironment for cell growth and function. For instance, lyophilized human fascia patches were reinforced with PLLA/PGA braid to control their mechanical properties for the repair of rotator cuff [179]. In another study, Cooper *et al.* [180] used multifilament PLLA fibers, fabricated into 3D square braids, for ACL regeneration in rabbits and demonstrated that the initial tensile strength of the scaffolds was similar to that of native tissue. Furthermore, after 12 weeks of implantation, the cell-seeded scaffolds revealed excellent tissue infiltration and vascularization. Kimura *et al.* [181] developed fibronectin coated braided PLLA scaffold to improve cell adhesion for ACL regeneration. The hydrogel gelatin encompassing basic fibroblast growth factor (bFGF) was inserted in the defect site of rabbit models, between two fibronectin coated PLLA scaffolds and wrapped with a collagen membrane where a tube shape was formed initially in the femur and tibia of the animal. They observed significant bone regeneration in the tunnel and ACL tissue regeneration in the joint cavity [148]. Furthermore, they concluded that the controlled release of bFGF, which improved cell migration, promoted collagen production and enhanced the mechanical properties of the regenerated ACL tissue. It has been mentioned before that the fiber materials, morphology of the scaffold, and the interactions between the fibers play critical roles in the functionality of the engineered grafts [132]. Three to five aligned bundles of electrospun fibers of PLLA nanofibers were braided and seeded with hMSCs to fabricate a tendon-like construct [133]. This construct could provide further degree of flexibility to control the mechanical characteristics of scaffolds. Results showed that this novel scaffold could support both proliferation and differentiation of stem cells for tendon and ligament TE applications [133].

In musculoskeletal tissues, skeletal muscles also play key roles in human body: from controlling bones movement to protecting abdominal viscera and active contraction in respiration. Therefore, skeletal muscle damages can result in severe motor dysfunctions that seriously affect the quality of life. Autografting of muscle tissues is one of the current treatments for skeletal muscle injury. Limited availability of donor tissues and the high chance of rejection or infection after surgery reduce the outcome of surgical autografted tissues [182]. Thus, implantation of allogeneic myogenic cells including satellite cells and myoblasts is used to help increase the regenerative capacity of skeletal muscles [183]. However, the challenges of allogeneic transplants including the risk of disease transfer and immune responses to the replaced tissues are very complicated [184]. Therefore, designing and engineering functional muscle tissues that include multinucleated, post-mitotic fibers is vital to reconstruct the damaged tissue. Engineered skeletal muscle tissues can be used in other applications as well: for instance drug screening [185], biorobotics (muscle actuators) [186], biosensing [187], food industry (engineered meat) [188] and energy harvesting (energy source for implanted medical devices) [189]. Studies have focused on creating muscle tissues from living progenitor cells, cultured on a biodegradable scaffold to improve the formation of organized myofiber bundles in the reconstructed tissues [184, 190]. However, regenerating the highly dense and aligned myofibers is still challenging as the old fabricated tissues failed to structurally and mechanically mimic the native tissues. In native muscle tissue, myofibers with their organized architecture and alignment are responsible for the contractile forces enabling a high degree of the muscle movement [191, 192]. Therefore, mimicking the same physiological environment could be a key for the success of muscle TE. To address the importance of the fibers alignment and anisotropic structure of these tissues, some attempts have been made to develop unidirectional fibers in the form of nanofibrous scaffolds [193–195] or 3D aligned tubular porous scaffolds [196]. In one study, 3D aligned tubular porous scaffold containing aligned nanofibers inside the pores was developed by Jana *et al.* [197] that mimicked the native muscle structure. They showed that this structure could mimic the native muscle tissue structure. They used aligned chitosan-PCL nanofibers arranged co-axially with the aligned microscale chitosan scaffold to construct a laminar section of the hybrid scaffold, which mimicked the required myogenic environment. Following culturing the scaffolds with cells for 6 days, the nanofibers and scaffold bands organized the C2C12 mouse myoblast cells along the direction of the fibers. This aligned nanofibrous scaffold guided the cell alignment and facilitated the formation of a compact assembly of myotubes. Cells cultured

on the hybrid substrate expressed higher levels of myogenic differentiation genes associated with myogenin and myosin heavy chain compared to control substrates. In another study, Wang *et al.* [196] studied the application of hydrogel composites reinforced with aligned yarn for skeletal muscle TE. Composite of PCL/silk fibroin/ polyaniline (PANI) with core/shell aligned yarns was embedded in photocurable hydrogel (PEG-co-PGS), and the C2C12 cells within 7 days after culture showed the alignment and at longer culture time the formation of 3D elongated myotubes. Ostrovidov *et al.* [104] also showed enhancement of aligned myotubes formation on nanofibrous scaffolds by applying electrical stimulation. They fabricated electro-conductive, aligned electrospun fibers of gelatin reinforced with different concentrations of multi-walled carbon nanotubes (MWNTs) (20% gelatin fibers combined with 0.5mg/ml and 5mg/ml MWNTs) and cultured C2C12 myoblast cells on them. The presence of MWNTs significantly increased the mechanical properties, and after electrical stimulation of myotubes, the expression of mechanotransduction related genes was also upregulated. Ladd *et al.* [198] also designed a dual nanofibrous scaffold system of PCL/collagen and PLA/collagen onto the opposite ends of a drum to create a scaffold with 3 regions for muscle-tendon junctions (MTJs) regeneration. This scaffold shows a gradual mechanical property suitable for force transfer from muscle to tendon across the entire length of the muscle-tendon unit.

11.4.2 Muscular Tissues

Skeletal muscle tissues from the category of musculoskeletal tissues were discussed in the last section. Another category of muscular tissues is the heart valve tissues. Replacements of heart valves are engineered with the aim of overcoming the lack of intrinsic potential growth to current non-viable prosthetics. These tissue-engineered heart valves could potentially be permanent replacements in the surgical repair of pediatric valvular lesions. To establish an *in vitro* model, with a combination of cells and scaffolds with broadly tunable anisotropic and elastomeric properties, various fibrous constructs and fabrication techniques have been used [96, 199–202].

To engineer functional heart valve leaflets, the scaffolds should (a) mimic the anisotropic mechanical properties and elasticity of native heart valve leaflets [202, 203], (b) have a fibrous structure containing aligned fibers, resembling the microstructure of the native tissue [204, 205], (c) have elastic deformation and flexibility similar to native tissues [206, 207], and (d) possess controlled degradation and support tissue regeneration at a rate to maintain structural stability [208, 209].

With advances in TE, many studies have attempted to fabricate more robust and structurally similar valves using various polymers, decellularized tissues and hybrid scaffolds. Several fabrication techniques including electrospinning [96, 199, 200, 210], microfabrication (i.e. laser ablation, molding [201, 211], bioprinting [212, 213]) and jet-spinning [92] have been used to fabricate single or multilayered scaffolds for heart valve TE. In addition, natural hydrogels (e.g. fibrin gel [214], gelatin [199, 212] and hyaluronic acid [215]), and synthetic polymers (e.g. PGS, PCL, poly-4-hydroxybutyrate (P4HB), PEG [96, 199, 200, 210, 216, 217]) have been used/synthesized because of their proper material integrity to provide sufficient mechanical characteristics for the engineered leaflets.

Mayer and colleagues [218, 219] pioneered the use of synthetic polymers for TE heart valve. They implemented fibrous scaffolds composed of PLA woven mesh sandwiched between two non-woven PGA mesh sheets and seeded them with autologous myofibroblasts and endothelial cells [220, 221]. The scaffold's shrinkage, possibly due to the high stiffness of the scaffold, was reported within several months after implantation. In addition, the slower rate of scaffold's degradation, with respect to the rate of tissue growth on the scaffold, was another potential reason for the scaffold shrinkage leading to a considerable regurgitation of the blood during diastole. In one of the very early studies with fibrous scaffolds by Sodian and coworkers [222] they fabricated synthetic based bioabsorbable trileaflet heart valves which were seeded with autologous myofibroblasts and endothelial cells. The constructs were grown for 14 days in a pulse duplicator *in vitro* system under gradually increasing flow and pressure conditions. The non-woven PGA mesh (thickness 1.0 mm) was coated with a thin layer of P4HB [93] by dipping into a THF solution (1% w/v P4HB). A continuous coating and physical bonding of adjacent fibers was achieved following solvent evaporation. Using the PGA/P4HB composite scaffold material, trileaflet scaffolds were fabricated by using a welding technique. The constructs were then cold gas–sterilized with ethylene oxide. Since PGA degrades faster than P4HB, the composite scaffolds remained stable longer for the implanted period (approximately 4 weeks versus 8 weeks, respectively). Amoroso *et al.* [223] fabricated electrospun fibers composed of poly(ester-urethane) urea (PEUU) by optimizing the electrospinning parameters and leaflet shape design. These fibrous PEUU scaffolds mimicked the heart valve anisotropic mechanical properties.

Over the past 10 years, PGS has been introduced as a scaffolding material for TE due to its desirable mechanical properties. However, the use of PGS in TE is limited by difficulties in casting micro- and nanofibrous structures, due to high temperatures and vacuum required for its curing and its

low molecular weight to fabricate electrospun fibers [224]. Therefore, the polymer was mixed with commercially available polymer PCL [96, 209] to develop microfibrous scaffolds, from blends of PGS and PCL, using a standard electrospinning set-up. At a given PGS/PCL ratio, a higher voltage resulted in significantly smaller fiber diameters (reduced from 4 to 2.8 μm). Further increase in voltage resulted in the fusion of fibers. Similarly, higher PGS concentrations in the polymer blend resulted in significantly increased fiber diameter. To address the lack of the anisotropic structure of these scaffolds, in a recent study, Masoumi *et al.* [96], used a directional electrospinning technique to fabricate fibrous PGS/PCL scaffolds containing aligned fibers, which resembled native heart valve leaflet ECM network. In addition, the anisotropic mechanical characteristics of fabricated scaffolds were tuned by adjusting the PGS/PCL ratio to mimic the native heart valve's mechanical properties. The valvular cells were also biochemically active in producing heart-valve-associated collagen, vimentin, and smooth muscle actin as determined by gene expression. The fibrous PGS/PCL scaffolds seeded with human valve interstitial cells (VICs) mimic the structure and mechanical properties of native valve leaflet tissue and could potentially be suitable for the replacement of heart valves in diverse patient populations.

To engineer an ideal heart valve, researchers have developed a biohybrid scaffold with non-cross-linked decellularized bovine pericardium extracellular matrix (DBP-ECM). This hybrid scaffold was coated with a layer of PCL-chitosan (PCL-CH) nanofibers, which displayed robust mechanical properties appropriate for heart valve TE. Surface and functional studies demonstrated integration of PCL-CH to the DBP-ECM with enhanced bio and hemocompatibility. The study claims that DBP-ECM is an attractive biocompatible component but has weak mechanical properties and rapid degradation. Therefore, they modified it with synthetic polymer (PCL-CH) to enhance its mechanical properties [225].

The hybrid structure is favorable due to the existence of both synthetic polymers, which provides the mechanical stability and hydrogel component that provides a more cell-friendly environment for cell growth and tissue regeneration. Recently, Eslami *et al.* [199] used electrospun PGS/PCL microfiber scaffolds for mitral valve regeneration, which possess sufficient mechanical properties for heart valve engineering and are covered with hydrogel layers made from methacrylated hyaluronic acid and GelMA. Sheep mitral VICs were encapsulated in the hydrogel and evaluated in different combinations such as hydrogel-only, PGS/PCL scaffold-only, and composite scaffold.

The third type of muscular tissue is the smooth muscle tissue, which can be found extensively in the blood vessels structures. Electrospun fibrous tubular

conduits are the most applicable scaffolds for vascular tissue regeneration due to resemblance with the hollow structures of vascular tissues (Figure 11.9). For example, non-woven, biodegradable vascular prosthetic composed of submicrometer fibers was fabricated using electrospinning for TE of vascular grafts [226]. Natural and synthetic polymers such as collagen [227], fibrin [228], elastin [229], polytetrafluoroethylene (ePTFE) [230], Dacron

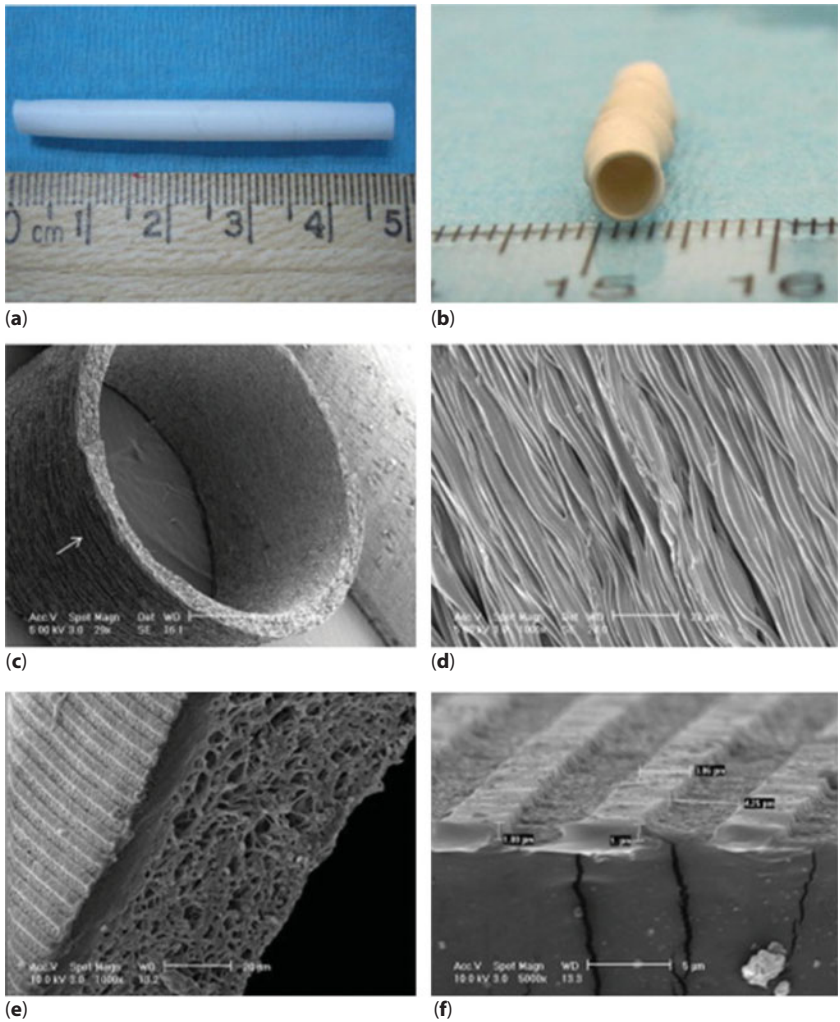

Figure 11.9 (a, b) An electrospun PU graft with a length of 48mm and diameter of 4 mm. The SEM micrographs (c-e) show the alignment of the fibers and cross-sectional images of luminal structure. In panel f, ridge width is 3.6 μm and channel width and depth are 3.9 μm and 0.9 μm, respectively. Adopted with permission [99]. Copyright 2014, Elsevier.

[231] and PU [232] have also been used in vascular TE [24]. However, natural polymers like collagen and elastin suffer from low mechanical properties [233] and synthetic polymers like PLLA and PGA with long degradation time do not provide a hostile environment for cell attachment and growth [226, 234]. Therefore, the electrospun fibers from blend of synthetic and natural polymers were developed to integrate the benefits of both and eliminate the potential issues with the sole use of each component. For instance, Stitzel *et al.* [235] used ternary blend of 3 different polymers (PLGA-collagen-elastin) to fabricate nanofibrous tubular scaffolds. The fibers blend showed adequate mechanical properties and suitable bioactivity.

In another work, a tri-layer tubular conduit was fabricated from blends of polydioxanone (PDO) and natural polymers like gelatin and elastin. This tubular conduit had 20cm length and 4mm inner diameter and its mechanical properties were similar to complex matrix structure of native arteries [236]. They showed that tubular conduit could be fabricated with different layers of randomly oriented or unidirectional fibers as inner and outer layers which influenced the cell growth and alignment [236]. Fu *et al.* [237] also produced fibers of gelatin/PCL and collagen/PLCL for generating vascular tissues. Due to the presence of natural proteins, this hybrid fibrous construct showed high hydrophilicity and cell attachment. After *in vivo* studies in mouse, the tissue growth on the engineered vessels of collagen/PLCL was relatively homogeneous and the Young's modulus of the implanted tissues was greater than gelatin/PCL scaffolds. In a similar study by Nannan *et al.* [238], the core-shell fibers of PCL/collagen were used to fabricate engineered vascular tissue. In that structure, PCL as a core material provided the mechanical strength and collagen as a shell improved the vascular cell adhesion. Most of the commercial vascular grafts are fabricated by weaving and knitting polyesters such as Dacron [239]. However, to improve the biocompatibility, the surface property of these constructs was modified by silk fibroin and other proteins like collagen. Yang *et al.* [240] combined silk yarns and polyesters and showed their better mechanical properties and cytocompatibility compared to ePTFE implants.

11.4.3 Ocular Tissues

Cornea is the outermost layer of human eye with unique structure, which provides several fundamental functions in ocular system such as transparency for light refraction and transmission and chemical and mechanical protection of the inner parts of the eye. Approximately 10 million people with corneal blindness have been identified that are suffering from trauma

or bacterial and viral infections [241]. The second most common eye disease in the world is related to cornea that leads to blindness [242]. Similarly to other tissues, current treatment to treat corneal dysfunction is transplantation. However, long-term survival of the transplanted tissue can be as low as 64% because of immune graft rejections or infection [241, 243]. With the goal to mimic the structure of native cornea including 300–500 layers of aligned collagen fibrils, corneal TE provides a new possibility for the tissue treatment [242]. In order to provide fibers with similar structure (diameter, spacing, morphology and orientation) and mechanics to corneal tissue, electrospinning has been widely used to generate native-like tissues. The transparency and anisotropic mechanical properties of cornea rely on unique and uniform structure of collagen fibrils with small diameter, regular spacing and orthogonal orientation [244]. Yan *et al.* [245] showed that uniaxially aligned blend fibers of gelatin and PLLA, compared to randomly oriented fibers, could induce the keratocytes alignment along the direction of the fibers and induce tissue ingrowth. Salehi and coworkers [98, 246, 247] demonstrated that nanofibrous scaffolds of aligned fibers fabricated from the PGS/PCL blend with different ratios showed promising cell and immune-compatibility with the corneal cells and were nontoxic and inert in contact with leukocytes. They also showed that uniaxially aligned fibers could induce the growth of corneal cells on the scaffolds along the fibers. Blending of chitosan and PCL also showed promising results during the culture of corneal endothelial cells [248]. Since these two materials express different characteristics, the blend of chitosan and PCL presented a suitable scaffold for cells to express the tight junctions and generate the extracellular matrix protein cultured on the substrate. Sharma *et al.* [249] also showed the application of PCL nanofibrous scaffold as a synthetic stromal substrate for limbal epithelial cell (LEC) culture. Epithelial cells adhered to 150nm PCL fibers and produced a uniform cell sheet.

Hydrogels reinforced with nanofibers also showed a promising result in cornea TE. Hydrogels are favorable materials for TE because of their high water content, cell compatibility, and nontoxicity; however, they suffer from weak mechanical properties which can be enhanced using nanofibrous mat integrated within the structure [250]. Tonsomboon and Oyen [251] fabricated transparent fiber-reinforced hydrogels by embedding the electrospun gelatin nanofibers within alginate hydrogel (Figure 11.10). The mechanical properties were compared before and after cross-linking of gelatin fibers and alginate matrix. Electrospun gelatin nanofibers without cross-linking could also improve the tensile elastic modulus of the hydrogels; however, as explained before in other TE applications, their lack of sufficient mechanical strength must be compensated by using integrated nanofibrous mat.

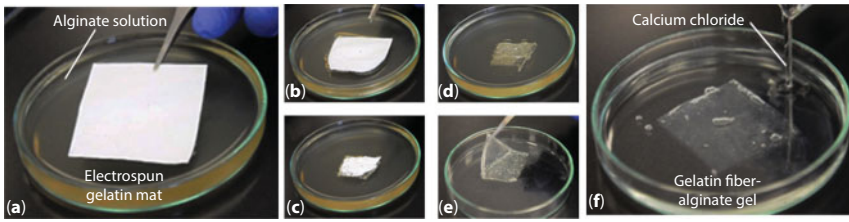

Figure 11.10 Fabrication of gelatin fiber reinforced alginate hydrogel. (a) Electrospun fibers were submerged in the alginate solution. (b-e) The steps of soaking, wetting and taking out from the alginate solution. (f) Alginate was cross-linked by $CaCl_2$ solution. Adopted with permission [251]. Copyright 2013, Elsevier.

Retina is another important part of the eye tissue. Age-related macular degeneration (AMD) and retinitis pigmentosa are two common retinal diseases diagnosed by the progressive degeneration of the retina and loss of the function of photoreceptor cells [252]. Over 30 million patients around the world are diagnosed with retinal degeneration [253]. Many different approaches such as administration of growth factors, gene therapies, and antiangiogenic therapies have been tested so far to delay the disease progression. However, the promising treatment for the late-stage retinal degeneration is to transfer the retinal stem or progenitor cells to the subretina or transplantation of retinal pigment epithelial (RPE) monolayer [254, 255]. To replace the RPE layer, several studies have been reported mainly on developing a suitable scaffold or substrate to maintain the RPE monolayer or mimic the native tissue structure *in vitro*. For example, Liu *et al.* [256] examined the influence of topography on RPE cell behavior and transplantation subretinally in rabbit by a planar film versus increasing electrospun fiber diameter (from nano to micro) of poly (ethylene terephthalate) (PET) and PLCL. They observed that RPE on 200nm fibrous samples could make a monolayer with pigmentation and uniform hexagonal tight junctions [256].

In another work, Warnke *et al.* [257] fabricated ultra-thin nanofibrous scaffolds from collagen type I and PLGA by clinical-grade needle-free electrospinning process. These nanofibers were structurally similar to fibrillar structure of the native inner layer of human Bruch's membrane (BM). The natural human BM is a 4-μm thick tissue, which separates the RPE monolayer from the underlying choriocapillaries. The function of BM is to physically support RPE cell adhesion, migration and differentiation. In this study, Warnke *et al.* [257] revealed the growth of human RPE on the pre-engineered artificial BM. Cells formed a monolayer with a polygonal

shape and abundant sheet-like microvilli on their apical surfaces and could build tight junctions and express the RPE65 protein.

One of the treatments for AMD disease is to deliver retinal progenitor cells (RPCs) to regenerate diseased retinal tissue. However, after injection, massive cell loss happened and RPCs did not stay alive [254, 258]. Recently, tissue-engineered scaffold showed improvement in the mouse RPCs (mRPCs) survival and enhanced the efficiency of integration of delivered mRPCs in host retinal tissue [258, 259]. In a study by Chen *et al.* [260], chitosan-graft-PCL/PCL (CS-PCL/PCL) hybrid scaffolds were developed to culture the mRPCs for 7 days. The real-time quantitative polymerase chain reaction results showed that the cells cultured on this scaffold could differentiate towards neural retina. Zhang *et al.* [261] also investigated the effect of blended nanofibrous scaffold of silk fibroin and PLCL on the biological behavior of retinal progenitor cells. These polymers mixed in 1:1 ratio showed the best cytocompatibility and the cells expressed the genes related to retinal neurons such as rhodopsin-positive photoreceptor cells.

The concept of cell transplant for photoreceptor cells in neural retina and for glaucoma disease treatment demonstrated a good integration and restoration of function of the cells. However, cell delivery into the ganglion cell layer is a fairly difficult process and cells are unable to stretch their axons toward the optic nerve head due to the changes in guidance molecules (Netrin-1 and Slit-2) in retina. In fact, the axon projection requires heparan sulfate expression in the neural retina to interact with these guidance molecules [262]. Tissue engineered scaffolds could mimic the retinal neurite patterning. Kador *et al.* [263] fabricated nanofibrous scaffold of PLA to guide the radial growth of retinal ganglion cells (RGCs) axons similar to retina tissue. They showed that the axons were aligned along the direction of scaffolds fiber (81%) similar to native tissue's nerve fiber layer. After transplanting of cells on retinal explants, they followed the radial orientation of the host retinal nerve fibers. The first advantage of using radially aligned fibers in this work was the extension of RGCs along the fibers, the second was guiding the cells towards the center, and the third was stopping them at the center point of the scaffold. This structure resembled the optic nerve head.

11.4.4 Nerve Tissue

Nerve damages occurring after trauma or surgery usually result in substantial injury and disability [264]. The "gold standard" approach to treat nerve imperfections is transplantation of the autologous nerve tissue. Despite significant development in transplantation method, it is restricted

by noteworthy donor site morbidity, limited harvest positions and size difference between the graft size and the recipient [265]. To overcome these limitations, various kinds of biological and artificial nerve conduits have been fabricated and have shown relatively successful outcome [266]. In order to enhance the rate of nerve regeneration, nerve conduits need to have basic structural and mechanical properties. To fabricate a functional construct, the nerve conduits should be degradable, durable to avoid collapse, resist the pressure imparted by surrounding tissues and support surgical operation, and must prevent inflammatory reactions to support the nerve regrowth. While there is an effective exchange of nutrients and waste from the nerve conduits wall, they should also prevent infiltration of cells and biological factors which hinders neural regeneration [267, 268]. In the nerve surgery, the tubular conduits usually are used when direct suturing of two opposing nerve stumps is not possible and use of degradable scaffolds is one way to bridge the damaged nerve gap and to enhance nerve regeneration [24].

Textile technology has been used widely to develop various kinds of neural conduits with desired architecture and mechanics that mimic the topographical structure of nerve ECM [29]. Among these techniques, electrospinning is the most common one that has been adapted to fabricate nanoscale fiber based conduits with different architectures and structures [269]. Chew *et al.* [270] developed nerve conduits with dimensions of 3.96 to 5.08μm from poly (ε-caprolactone-co-ethyl ethylene phosphate) (PCL-EEP) using electrospinning technique in order to fill a 15mm gap in the rat sciatic nerve defect and showed that full regeneration occurred after 3 months of implantation. Moreover, they showed that the rate of nerve regeneration was enhanced via introducing aligned fibers oriented towards the axis of the nerve conduit. Aligned fibers could significantly improve Schwann cell proliferation compared to randomly oriented fibers in rat nerve defect models as it guides the cellular structure in directional fibers, thus improving the cell-cell signaling and regeneration of nerve tissues in a systematic manner [271].

Quigley *et al.* [272] designed nerve conduits using combinations of different fabrication techniques and materials. They first made a lumen from knitted PLA fabric and then coated it with electrospun PLA nanofibers to control the pore size, important for nerve conduits. In the next step, to improve neuroprotection, stimulation of axonal growth and Schwann cell migration, knitted PLA lumen was filled with aligned PLGA fibers supported by a neurotrophin-enriched alginate hydrogel. Results demonstrated that fabricated PLGA fibers supported Schwann cell migration and neuron outgrowth [272]. Ichihara *et al.* [273] fabricated a nerve guide tube

using braided PLLA monofilaments and PGA multifilament yarn scaffolds coated with collagen for the healing of long nerve defects in beagle dogs. Yang *et al.* [274] designed nerve conduits based on aligned fibrous silk fibroin cast from fibroin solution with eggshell-like microstructure and showed that the scaffolds had higher mechanical and permeablity characteristics essential for nerve regeneration. The grafts were used to bridge a 10mm gap in sciatic nerve defect in rats and to promote the peripheral nerve regeneration. *In vivo* studies revealed that fabricated nerve conduits that were comprised of aligned fibers in the inner layer of the constructs improved nerve regeneration [270]. Yao *et al.* [275] showed a significant difference between the length of neurite on aligned fibers compared to randomly oriented fibers of PCL.

Braiding technique with capability to develop tubular structures, off-the-shelf availability, high flexibility and radial compressive strength as well as ability to support the dimensional stability is potentially a successful approach for engineering nerve conduits [86]. Inada *et al.* [276] applied this technique to develop a collagen coated PGA tube filled with a collagen sponge for the regeneration of large peripheral nerve defects. In the first clinical study on nerve regeneration, fabricated PGA-collagen nerve guide tube showed successful revival of muscle action potential and withdrawal of distal latency. In another study, multilayer biodegradable micro-braided PLA nerve conduits were developed to bridge a 10mm nerve gap in the rat sciatic nerve [277]. They reported an effective regeneration of the nerve system throughout the gap after 8 weeks implantation. Wang *et al.* [91] evaluated a novel PLGA conduit comprising of an outside dense layer and an inside porous scaffold to support peripheral nerve regeneration. While the main role of the outside layer was to maintain the nerve regeneration as well as compression performance, the major role of the inside layer was to replicate the matrix bridge architecture in the nerve regeneration process. Results demonstrated that this two-layer fabric had outstanding compression performance, which made it an ideal construct for nerve TE.

In another report, the effect of fibers alignment on neural stem cells (NSCs) arrangement and potential guidance of the cellular alignment was studied. The study showed that the aligned topography of scaffolds enhanced the efficiency of neuronal differentiation, which was due to the increase of canonical Wnt/β-catenin signaling (signaling by the Wnt family of secreted glycolipoproteins via the transcription co-activator β-catenin)[278], translocation to the nucleus and accumulation of cytosolic β-catenin [95]. In fact, nuclear β-catenin links to the TCF/LEF promoter region and this binding activates the gene expression and induces neuronal differentiation of NSCs [279]. Rearrangement of the cytoskeletal proteins can transform the

mechanical signals into the intracellular signals. Thus, alignment of the neurites along the fibers seems to be complex and more related to the contact cues such as the density and amount of the protein deposition on aligned nanofibres that subsequently improves the scaffold topography [280].

It has been reported that apart from mechanical and chemical cues, electrical stimulation can also guide stem cell fate morphology. The electrical stimulation can be applied by using conductive materials as substrates for tissue regeneration or by applying external electrical forces during neural tissue regeneration. For example, aligned core-shell nanofibres of conductive polymer filled with nerve growth factor (NGF) in the core and PANI in the shell were fabricated by coaxial electrospinning. Applying a constant voltage along the fibers stimulated pheochromocytoma 12 (PC-12) cells attached to these conductive fibers and differentiated them into neuron-like cells. Interestingly, the gradual release of NGF from the conductive core–shell nanofibers was enhanced following electrical stimulation [281].

11.4.5 Skin

Skin as the largest organ in the human body protects the internal organs and body against the invasion of pathogens and excessive water loss. Therefore, damage to this vital barrier can lead to loss of integrity and function of internal organs. Currently, skin autografts are the most used products for the standard treatment of large skin wounds. However, as with other tissues, it is limited to accessible suitable donor for autografting. The appropriate grafts should cover the wound without any immune response, help the process of healing with less pain, and avoid the formation of scar tissue [239]. Tissue-engineered skin grafts are promising treatment and commercial products such as Epicel®, Dermagraft® and Apligraf® are currently available in the market. However, the current products suffer from high cost, short shelf-life, and poor mechanical properties while handling in a surgery room [95, 282].

Nanofibrous scaffolds have been used for successful treatment of wounds or burns of a human skin. Hemostatic devices made of nanofibers could also present unique characteristics and several functions such as stopping bleeding, measuring the pH in the wound, and monitoring the epidermal wound condition [24, 283, 284]. In one study, short nanofibers were directly sprayed onto the wound as a wound dressing and their structure promoted the regeneration of new skin while preventing scar tissue formation [62]. The optimum pore size for randomly oriented fibrous mats for wound dressing is from 500nm to 1mm. It can capture the aerosol particles and protect the wound from bacterial penetration. Other properties,

such as high surface area in the range of 5–100m^2/g, are efficient for permeability to oxygen, absorbing fluid and preventing fluid accumulation at the wound site [62, 285].

Synthetic polymers have been used to fabricate skin grafts from nanofibrous scaffolds. However, poor cell interactions with polymers like PCL, PLLA and PLGA need to be improved by surface treatments. Modification with ECM proteins such as collagen and fibronectin is a common technique to improve cell adhesion to the scaffolds. Polymer solution blended with natural materials or bioactive molecules (such as collagen, gelatin, fibronectin and chitosan) also was used as an alternative scaffold to improve cell attachment to nanofibrous scaffolds for skin regeneration [101]. Bacakova *et al.* [286] showed efficacy of PLA nanofibrous scaffold with fibrin nanocoating for skin regeneration. Fibrin has been well-known as a component in most skin substitutes and treatment of skin injuries. Fibrin coating enhanced the stability of cells morphology on the scaffolds after 14 days of culture. In addition, cell spreading, mitochondrial activity, and cell population density were improved after adding ascorbic acid in the cell culture medium. Ascorbic acid enhanced the expression of collagen I and deposition of collagen in human dermal fibroblasts [286]. In contrast to other tissues, in skin regeneration the uniaxially aligned nanofibres are not as effective as randomly oriented or radially aligned scaffolds due to the irregular shape of the wound. Xie *et al.* [287] showed that radially aligned nanofibrous sheets of PCL could be spun using ring type collector with a point electrode in the center. The PCL fibers with radial orientation could encourage the dural fibroblasts cells to express the collagen type I at a higher level than random fibers which is the main ECM component in dural matter. Cells also migrated from peripheral healthy tissue toward the central injured part, thus showing the potential of this scaffold as a wound closure [287].

To improve the antibacterial activity of PCL nanofibrous scaffolds Ahmed *et al.* [288] loaded fibers with whey protein concentrate (WPC). As a first effect, the degradability of PCL after modification by WPC was enhanced and that was helpful for further incorporating antibiotics in the fibers and gradual release. Tetracycline hydrochloride as an antibiotic model was loaded in fibers and the releasing pattern was much improved compared to pristine PCL. Silk fibroin nanofibrous scaffold also was modified for antimicrobial activity by immobilizing peptide motif named Cys-KR12 [289]. Song *et al.* [289] used immobilized peptide nanofibrous scaffolds for wound care purposes and wound dressing. These scaffolds showed antimicrobial activity against 4 types of pathogenic bacteria. Proliferation of keratinocytes and fibroblasts also was facilitated in contact with these modified substrates.

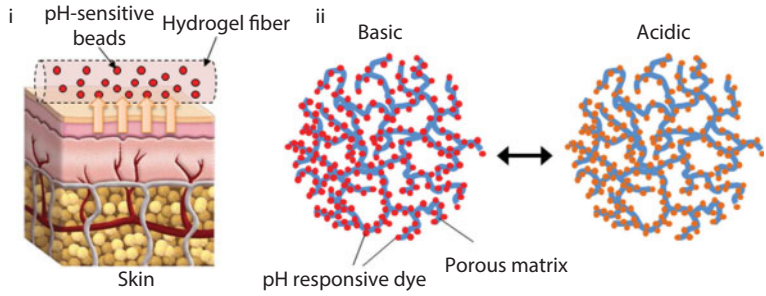

Figure 11.11 Schematic illustration of pH-sensing microfibers fabricated from pH-sensing beads embedded in hydrogel fibers. Beads are made of polyester containing pH-responsive dye. Adopted with permission [284]. Copyright 2016, Wiley.

Tamayol *et al.* [284] also showed a new application of nanofibers for wound healing. They fabricated pH-responsive hydrogel fibers made from alginate and loaded with pH-responsive beads. This system can be used to monitor the long-term pH in epidermal (Figure 11.11). Epidermal pH is an indicator of physiological condition of skin and can show the status of the healing process as well as bacterial infection. In chronic non-healing wounds the pH is different when healing process is going on from alkaline to acidic, respectively. This fibrous patch can monitor the skin disorder and can be used to fabricate wound healing dressings.

11.5 Summary and Prospects

In TE and regenerative medicine, biotextiles are promising materials due to their versatile properties and tissue-like microstructures. The microarchitecture can be easily tuned for optimized cellular distribution and permeability to nutrients, oxygen, and growth factors. Due to the anisotropic structure of nanofibrous scaffolds, fibers can guide cells alignment and also induce the differentiation process as the effect of both directions of fibers and stiffness of the construct. Moreover, fibers can play a role as carriers for cells, drug and biomolecules (e.g. growth factors) and by releasing specific molecules they facilitate vascularization in the final constructs.

One of the recent developments in fabrication of medical textiles is the generation of cell-laden fibers with tunable properties from various biomaterials. The initial cell-laden fibers were fabricated from hydrogels with poor mechanical strength. Although hydrogels could carry and deliver the cells and were useful for soft TE, they failed to provide sufficient mechanical strength for load-bearing tissues. Recently, composite cell-laden fibers

have been used, which provide independent compartments for constructs with tailored mechanical properties. Therefore, it is expected that further development of composite fibers will lead to realization of organized yet mechanically tunable constructs.

Textile-based tissues can also be used as a platform for drug screening or as *in vitro* disease models. Basically the ability of fibrous scaffolds for co-culturing multiple cell types loaded in or on the surface facilitates the interaction of cells with each other and also with the tested medicine. It is expected that similar to organ-on-a-chip platform, engineered tissues could serve as *in vitro* models for drug assessment. However, the scalability and ease-of-cell-patterning could make these a strong candidate for complementing organ-on-a-chip systems.

The increasing demand for development in fiber-based scaffolds, *in situ* TE applications can skip the disadvantages of *in vitro* TE. It will be easier to transfer the final product to the clinic for straightforward use. For example, cell-free fiber-based scaffolds such as tube-shaped fibrous scaffolds in nerve and vascular TE showed successful results in clinical studies. Therefore, the easy and low-cost fabrication can lead to cost-effective treatments.

All together some issues should be considered for further development of fibrous scaffolds named "biomedical textiles". For example, higher compatibility between fabrication techniques and types of biomaterials can lead to fabricate scaffolds with desired properties for regenerative medicine. Moreover, the integration of biomolecules in the constructs for gradual release is another important concept, especially in case of *in situ* TE.

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