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Textile Technologies and Tissue Engineering: A Path Towards Organ Weaving

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Abstract

Textile technologies have recently attracted great attention as potential biofabrication tools for engineering tissue constructs. Using current textile technologies, fibrous structures can be designed and engineered to attain the required properties that are demanded by different tissue engineering applications. Several key parameters such as physiochemical characteristics of fibers, pore size and mechanical properties of the fabrics play important role in the effective use of textile technologies in tissue engineering. This review summarizes the current advances in the manufacturing of biofunctional fibers. Different textile methods such as knitting, weaving, and braiding are discussed and their current applications in tissue engineering are highlighted.

Keywords

Biofabrication; Textile technologies; Fiber-based techniques; Biomaterials; Scaffolds; Tissue engineering

1. Introduction

Tissue engineering is a multidisciplinary enterprise that combines the principles of cellular biology, biomaterials, and engineering to address the current unmet demands for organ transplantation [1]. Fabrication of constructs with controlled mechanical properties, microstructure, and cellular distribution plays a crucial role in the engineering of functional tissues. Scaffolds made from synthetic or natural biomaterials are commonly utilized to provide mechanical support and three dimensional (3D) environments for cellular growth and function. Traditional methods for creating scaffolds including freeze-drying [2], particle leaching [3], and solvent casting [4] generate porous constructs with interconnected pores that are suitable for delivery of nutrients to the cells. However, the ability of these approaches for precise control over the spatial distribution of pore size and interconnectivity, mechanical properties, and structural properties is limited. Recently, advanced biofabrication methods such as bioprinting [5–8], stereolithography [9–11], self assembly of microgels [12, 13], and biotextiles [14–16] have emerged to produce complex 3D engineered tissues from living and non-living elements with exquisite control over the resulting scaffold microarchitecture and cellular distribution.

Commercial biotextiles (e.g., TIGR® Matrix, ULTRAPRO™, and INTERGARD™) are currently used as medical implants for treating pelvic organ prolapse, hernia, and vascular diseases. Recently, textile technologies have been utilized for biofabrication of fibrous scaffolds for various tissue engineering applications [14, 16–18]. Such technologies include

weaving, knitting, braiding, embroidering, and electrospinning. The versatility of textile structures allows for tailoring their architecture by controlling the fiber size and orientation, pore size and geometry, pore interconnectivity, total porosity, and surface topography. All these properties are important for controlling the physical properties and cellular behavior of the engineered constructs. In addition, by utilization of cell-laden fibers during the assembly process, the cellular distribution can be finely controlled. In this review, we will primarily focus on the current advances in the textile-based fabrication methods for tissue engineering. Recent technological advances in the manufacturing of biofibers as building blocks of biotextiles will be highlighted. We will then explore emerging applications of biotextiles for tissue engineering and regenerative medicine.

2. Biofunctional Fibers

Fibers are building blocks of biotextiles and their properties play an important role in the physiochemical properties of the final construct. In this section, we grouped biofunctional fibers into four major categories of synthetic, hydrogel, natural, and composite fibers. Table 1 summarizes these categories and provides a comparison between them.

2.1. Synthetic fibers

Synthetic polymers are widely used for the fabrication of scaffolds in tissue engineering and regenerative medicine. Examples include vascular prostheses that were made from poly(tetrafluoroethylene) (PTFE) seeded with bone marrow stem cells [19], cartilage scaffolds made from poly(glycolic acid) (PGA) yarns and seeded with porcine articular chondrocytes [14], and tissue engineered bladders fabricated from poly(DL-lactic-co-glycolic acid) (PLGA) matrix [20]. Synthetic materials have also been used in the form of micro- and nanofibers as they mimic the intricate fibrillar microstructure of the natural extracellular matrix (ECM) [21]. Several approaches have been developed for creating micro- and nanofibrillars from synthetic biomaterials. Electrospinning and blow spinning are low-cost and robust methods for creating nanofibers with dimensions as small as 10 nm [22, 23]. Electrospun non-woven mats have been used to create biodegradable nanofibrous structures for cardiovascular tissue engineering [24], flexible electronics [18], and skin tissue engineering [25]. Blow spinning is an alternative method for making non-woven fibrous structures with nanometer diameter fibers [26]. This method offers the advantages of higher production rate compared to electrospinning [26]. Both electrospinning and blow spinning approaches can be used to generate scaffolds with pore dimensions that are much smaller than the average size of the cells; thus, limiting cellular infiltration [27].

Inspired by the process of protein self-assembly, nanofibers are now being formed from oligomeric peptide, nucleotide and nonbiological amphiphilic building blocks [28]. Although this is a promising approach, the self-assembly process occurs under conditions that are intolerable to cells, impeding the incorporation of cells during the fabrication process.

To fabricate fibers with micron-size dimensions, other methods including meltspinning [29, 30] and microfluidic spinning [31, 32] have been utilized. Such methods enable generating

grooves on the surface of the fibers, making the suitable for directing cellular alignment and growth [30].

The choice of materials varies from non-degradable polymers such as polypropylene (PP) [33] and PTFE [34] to degradable polymers such as PGA [35] and PLGA [31]. These fibers can be used in the form of monofilament or multifilament twisted or braided yarns for the biofabrication of scaffolds and biotextiles. It has been shown that the size and surface topology of monofilament fibers can modulate the orientation and organization of cells [30, 31]. Cells have shown to respond to the surface morphologies in nano- and microscales [36–39]. For instance, cells grown on PLGA fibers were mostly aligned along the fiber axis when seeded on smaller diameter fibers (<30μm) (Figure 1) [31]. Moreover, the surface texture on the fabricated fibers can control the cellular orientation and alignment [38]. It has been shown that the fabrication of monofilament fibers with microgrooves on their surface enhanced cellular orientation along the direction of the grooves [30]. Multifilament yarns, with similar surface topography as threads used in textile industry, have been assembled by means of commercial textile instruments for the fabrication of load-bearing tissue scaffolds and used in cartilage [40] and cardiac muscle tissue engineering [41].

Due to their high mechanical properties, synthetic biofibers are great candidates for creating load-bearing scaffolds for tissue engineering. In addition, the high strength allows their assembly using commercial textile machines. By varying the surface morphology and fiber diameter, cellular alignment and functions can be modulated. Key challenges towards cells encapsulation within these synthetic fibers include the harsh fabrication process of synthetic fibers and their commonly small pore sizes. Another major challenge for the use of synthetic fibers in tissue engineering is the lack of binding sites on these fibers'surface, which makes them not cell adhesive. Thus, surface treatment strategies such as adsorption of proteins, tuning the surface characteristics such as topography, energy and hydrophilicity, as well as coating fibers surface with ECM-based materials should be used to promote cellular attachment.

2.2 Hydrogel-based fibers

Hydrogels are 3D polymeric networks with high water content, which are formed from hydrophilic polymer chains. These materials have found many applications in tissue engineering as they provide a nurturing environment for cells to proliferate and grow [42–44]. Considering the importance of hydrogel-based constructs in tissue engineering, multiple fabrication processes have been developed to create hydrogel fibers with a wide variety of physical and biological characteristics.

Wetspinning is a widespread technique to fabricate hydrogel based fibers and consists of injecting a prepolymer into a crosslinking solution to create continuous solid fibers with diameters as small as 50 μm [45]. The fiber diameter can be controlled by changing the injection flow rate and the needle diameter. In general, a quick crosslinking process is desired if the crosslinker and prepolymer are both hydrophilic, else the prepolymer can diffuse into the crosslinking solution preventing the formation of mechanically stable fibers. Alginate is the most employed hydrogel for fabrication of wetspun hydrogel fibers due to its rapid crosslinking process by calcium chloride ($CaCl_2$) [46, 47].

Microfluidic spinning is an alternative approach, which has been recently used for fabrication of biofibers [15, 48–50]. Its operation mechanism is similar to that of wetspinning, with the difference of co-flowing the prepolymer and crosslinker co-axially in a microchannel. The hydrogel crosslinks as it flows through the channel and the fiber is completely formed at the exit of the microfluidic device. In this approach fibers with diameters ranging from ten to few hundred micrometers can be fabricated. Generally microfluidic spinning offers a better control over the fiber size and shape in comparison to wetspinning [42, 49, 51].

Microfluidic systems are robust and capabale of fabricating multicomponent fibers. For example, core shell fibers have been fabricated with this approach with the core contained cell-laden ECM-based proteins and the shell consisted of an alginate layer to protect the cells (Figure 1a–c) [15]. In another study, the position of the cells across the fiber cross-section was precisely controlled and hepatocytes were positioned between endothelial cells to mimic the native cellular distribution in human liver (Figure 1d–e) [48].

A typical challenge of working with hydrogel fibers is that they are not mechanically strong and rapidly dehydrate. However, overall hydrogel fibers hold great promise for fabrication of tissue constructs. These fibers can contain cells, bioactive molecules and drugs, making them useful for many applications such as soft tissue engineering, drug and cell delivery, and as implantable sensors. However, due to their limited mechanical strength, hydrogel fibers' handling and assembly using current textile technologies is not trivial. Strategies such as the use of reinforcing materials for enhancing the mechanical properties of the fibers have to be pursued to address this challenge. Additionally, special weaving looms capable of weaving in wet environment should be devised to prevent fibers from drying during the fabrication process.

2.3 Natural fibers

Naturally derived biomaterials such as proteins and polysaccharide-based materials have found extensive applications in tissue engineering due to their superior biocompatibility as compared to the synthetic materials. Collagen is the most abundant protein in the human body and is the main component of the ECM in connective tissues. Because of its unique properties such as excellent biocompatibility, tunable biodegradability, and being hemostyptic, collagen has been used as a popular naturally derived material in tissue engineering. The first known degradable sutures (catgut sutures) were made from purified collagen taken from the small intestine of ruminants [52]. Recently, collagen threads were manufactured by wetspinning and meltspinning methods [53–56]. The fabricated fibers were used for applications in neural and bone tissue engineering.

Chitosan is another attractive material that has a wide range of applications in tissue engineering due to its unique biological properties that include biocompatibility, biodegradability to harmless products, physiological inertness, excellent protein affinity [57, 58]. Chitosan also has antibacterial, haemostatic, fungistatic, anti-tumoral and anticholesteremic properties, which makes it an excellent candidate for drug delivery and wound healing applications [59]. Wetspinning has been the main approach for fabricating

chitosan fibers [60–62]. However other methods including electrospinning [63, 64] and interfacial complexation [65] have also been used for creating scaffolds made from chitosan.

Silk is a protein-based polymer that is spun into fibers by silkworms, spiders, scorpions, mites and flies [66]. Due to their high tensile strength, sutures made from silk have been used for a long time in ocular, neural and cardiovascular surgeries. For tissue engineering applications, silk fibers were braided and used as an autologous tissue engineered anterior cruciate ligament [67]. Using microfluidic spinning technique, silk fibers have been fabricated in vitro that possess similar mechanical properties of the naturally drawn silks silk fibers [68]. Naturally derived fibers are attractive materials for tissue engineering applications because of their excellent biocompatibility and inherent properties of biological recognition [21]. However, complexities associated with purification, immunogenicity, and potential pathogen transmission still remain major challenges for use of these materials in tissue engineering. Some of these challenges could be overcome by using recombinant protein expression technologies [69]. Moreover, combining naturally derived polymers together with synthetic materials can be another approach for addressing some these limitations.

2.4 Composite and hybrid reinforced fibers

Composite and hybrid fibers generally refer to a class of fibers that are fabricated from two or more individual constituent materials. In composite assembly, each material remains distinct and contributes to a specific function. In hybrid systems, however, the constituents can be mixed throughout the construct [46, 70, 71]. An example is hybrid fibers that were made from ultra high molecular weight polyethylene (UHMWPE) and polyvinyl alcohol (PVA)[70]. The prominent elastic properties and fatigue strength of UHMWPE enhanced the limited strength of the PVA hydrogel in tension, while the hydrogel itself contributed to the significant biocompatibility and resistance to wear which is essential to withstand the hoop stresses applied during frequent loading cycles. In a notable study, gold nanowires were added to the matrix of alginate scaffolds to enhance electrical conductivity (Figure 3a–d) [71]. It has been shown that such composite material promotes the cardiomyocytes function. As mentioned before, alginate is a strong hydrogel material that has been widely used for fabrication of hydrogel fibers using wetspinning or microfluidic spinning [47, 48, 51]. However, this material does not provide a nurturing environment for the cells to spread and function. To overcome this issue, more cell friendly materials such as chitosan [72], fibrin [73] and gelatin-based materials [16] have been blended with alginate to improve the cellular activity.

To overcome the challenge of low mechanical stability of cell friendly hydrogels, reinforcing materials such as carbon nanotubes and geraphene oxide have also been used [74, 75]. Another approach to improve the mechanical properties of the hydrogel fibers is to create composite fibers with a load-bearing component. In one study, composite fibers were made from a load-bearing core material, which was coated with a cell-laden hydrogel layer. Such fibers possessed the mechanical strength of the synthetic material while still providing the favorable environment for the cells to grow [16]. The method was cytocompatible and was utilized to coat single and multilayers of particle- and cell-encapsulated hydrogels on a

mechanically strong core fiber (Figure 3e–i). The fabricated fibers were strong enough to be assembled using textile techniques and the cells remained functional during the fabrication and assembly process.

Although the higher mechanical strength of composite fibers compared to pure hydrogel fibers allows assembling them using textile methods, the presence of two distinct phases may result in fiber delamination at the interface of its components. In addition, different degradation rates between the core and sheath layers can also affect the physical properties of the construct and can interfere with cellular migration and distribution.

3. Textile Technologies in Tissue Engineering

Textile technologies have reemerged as promising approaches for creating complex constructs from monofilament fibers and multifilament threads for various tissue engineering applications. In this section, a summary of three textile methods that allow controlling the microstructure, mechanical properties, and cellular distribution of the tissue construct is provided. Table 2 summarizes these methods and provides highlights the advantages and drawbacks of each method. It is worth noting that nonwoven constructs that are widely used in many areas of tissue engineering are out of the scope of this review. Comprehensive reviews on the application of nonwoven constructs in tissue engineering are provided by Anwarul *et al.* [76] and Pham *et al.* [77].

3.1. Knitting

Knitting is a well-established textile method for creating complex 2D and 3D structures from yarns that are interlaced in a highly ordered arrangement of connected loops. In the knitting process, yarns are drawn through a previous loop to form interconnected loops. Depending on the direction of the formed loops, the knitting process is classified into two major categories of weft and warp knitting [78]. In weft knitting, stitches from the same yarn are arranged horizontally (Figure 4a), while in warp knitting, stitches from the same yarn are arranged vertically (Figure 4b). Knitted constructs can be characterized by their course and wale, which are the number of rows passing across the width and length of the fabric, respectively. The number of wale per unit length of the fabric is a function of the density of needles (“gauge”), yarn size and type, and the applied yarn tension.

Depending on the knitting process, types of stitches, and the yarn material, fabricated constructs possess different mechanical and physical properties. Fabrics made from tuck stitches have larger pore size and are wider, thicker, and slightly less extendable than fabrics generated from regular stitches. Float stitches on the other hand provide directionality to the structure of the knitted fabrics [78, 80]. The warp-knitted structures show more flexibility and extendibility compared to the weft-knitted constructs [80]. However, the weft knitting offers superior control over the pore size, porosity, and fiber alignment in the construct [81]. Currently, there are automated and programmable machines that are capable of creating complex 2D and 3D fabrics in large scale. For example, “Tricot” and “Raschel” machines perform warp knitting while “flatbed” and “circular” machines perform weft knitting.

Knitted scaffolds have been extensively used to engineer or to repair damaged tissues and organs [16, 79, 81–85]. Mechanical properties and microstructure of the knitted structure are the two important parameters affecting the scaffold functionality. The pore size of the knitted fabric should be large enough (~100μm) to allow cellular ingrowth while maintaining the mechanical strength of the construct under the applied stresses. Knitted fabrics have also been employed as a reinforcing skeleton to provide structural support for a collagen or silk sponge with proper biological environment for tissue growth (Figure 4c–e). For example, knitted silk-collagen sponge scaffold has been seeded with human embryonic stem cells (hESC) and human mesenchymal stem cells (hMSCs) for tendon and ligament regeneration, respectively [79, 82]. In another study, scaffolds knitted from hydroxyapatite-coated silk yarns have shown enhanced osteoinductivity and osteoconductivity [84]. Although knitted constructs have been mostly used as a reinforcing structure, there are also reports of their use as a selectively removable template for creating autologous ECM scaffolds [86]. The process includes culturing cells on a knitted construct with desired microstructure and removing the knitted template after the ECM deposition of the cells. With the recent advances in the development of novel biomaterials, yarns can be made with controlled degradation profiles and mechanical properties.

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

3.2. Weaving

Weaving is one of the most ancient technologies developed by man for creating cloth [87]. In this textile method, the fabric is formed from two distinct sets of yarns, which are interlaced normally [88]. The lengthwise yarns are called warps and the weft (filling) passes through them in the lateral direction. The most common weaves include plain, satin, and twill (Figure 5a). In plain weave, each weft passes over one warp and then under the following warp and this trend will be reversed in the following row. In satin weave, warps are floating on top of a number of wefts and are more exposed in comparison to plain weave. In twill weave, on the other hand, the wefts are passed through the warps in a way that they are exposed in a diagonal fashion. Different weaves can change the flexibility and smoothness of the fabric. Another important factor that affects the looseness as well as the porosity of the generated fabric is the number of warps and wefts per square inch [89].

Weaving looms are simple and easy to use and are compatible with a wide range of materials. Consequently, the application of woven constructs has extended to multiple engineering applications including composite fabrication, fuel cell technology, and biomedical engineering. Woven structures are more flexible than knitted constructs but can endure less force in the in-plane direction. Moreover, woven fabrics are less porous than knitted structures and possess smaller pores. The in-plane mechanical properties can be

improved by interlocking multiple layers of woven fabrics for the applications that require load-bearing characteristics [90]. Moreover, the use of multiple layers allows for the fabrication of thick 3D structures.

Woven fabrics have been utilized as tissue engineering scaffolds or reinforcement mats in hydrogels to tune the mechanical properties of the construct. In a pioneering study, Moutos et al. developed a microweaving loom to assemble PGA yarns into fabrics [14]. They also interlocked several layers to create a load-bearing 3D structure. The reinforcement mat was embedded within chondrocyte-laden agarose gels for cartilage tissue engineering (Figure 5b). This work was later adopted by a number of groups which fabricated reinforcing structures from silk, poly(caprolactone) (PCL), and polypropylene[17, 91–95]. These studies have been mostly focused on mimicking the biomechanical properties of native tissues through the utilization of woven fabrics. Recently, researchers have tried to use weaving looms for controlling cellular pattern within a construct. For example, Onoe *et al.* devised a microweaving machine and assembled cell-laden hydrogel fibers to create complex constructs with controlled cell distribution (Figure 5c) [15]. In another study, wetspun cell- and bead-laden hydrogel fibers were created and then assembled using a custom-built weaving loom [46].

Hydrogel fibers are usually not mechanically strong, thus, the mechanical properties of the fabricated fabric will not be suitable for applications that require load-bearing characteristics. Our group has introduced the concept of composite living fibers (CLFs) with a load-bearing core and cell-laden hydrogel shell [16]. We assembled these CLFs using a weaving loom to create cell-laden fabrics. Weaving CLFs with mechanically strong core enabled us to control both cellular distribution and mechanical properties (Figure 5d).

Weaving allows fabrication of 3D constructs with tunable anisotropic mechanical properties that mimic the properties of several native tissues such as cardiac and cartilage. Weaving looms are easier to design in comparison to knitting systems for creating cell-laden structures with controlled mechanical characteristics and cell distribution. In addition, the weaving process is less mechanically harsh compared to other textile processes.

3.3. Braiding

A braided structure is comprised of three or more strands intertwined in overlapping patterns. A wide variety of 3D geometrical shapes with fine-tuned stable properties can be obtained through varying the arrangements of diagonally intertwined strands. Complex structures fabricated through braiding are differentiated from knitted or woven counterparts by the versatility they offer in axial and radial load-bearing properties, enhanced physical stability, damage tolerance and fatigue resistance in bending, torsion and traction, as well as improved abrasion resistance [51, 96–98]. A wide range of the medical textiles are manufactured using braiding technology including sutures, stents, nerve regeneration conduits, braided composite bone plates, scaffolds for ligaments tendons, and artificial cartilages [51, 98].

The high tensile strength and mechanical flexibility of braided structures have made them an excellent candidate for engineering of articular and connective tissues such as cartilage,

tendon, and ligament. Anterior cruciate ligament (ACL) is the most commonly injured intra-articular ligament of the knee [99]. Braiding technique has been used to develop numerous ACL grafts with biomimetic characteristics [34, 99–101]. It has been shown that the fiber materials, morphology of the scaffold, and the interactions between the fibers play critical roles in the proper function of the engineered grafts [102, 103]. A major challenge in ACL tissue engineering is regenerating articular cartilage with anisotropic and heterogeneous mechanical properties. Varying braiding angle, fiber density and number of layers, enable developing anisotropic mechanical and physical properties with adjustable gradient along any desired direction. By changing the porosity of the engineered graft from the two ends toward the middle region, cellular ingrowth can be enhanced while the mechanical properties of the engineered tissue are maintained [103]. Utilizing numerical tools, optimized fiber configurations that provide the biomechanical requirements needed to restore the knee function were determined [102].

Selection of proper fiber material is another important parameter that has to be considered in the fabrication of braided tissue constructs. Synthetic materials such as poly(lactic acid-co-ε-caprolactone (PLCL) [101] and poly(L-lactic acid) (PLLA) [99] or composite fibers made from synthetic and natural materials such as 50% type I collagen and 50% PVA [100] have been used for ACL tissue engineering. Synthetic materials provide the mechanical strength while the natural materials provide a more nurturing environment for the cells to grow and function.

Another well-recognized approach to enhance and direct cellular activities is to create nano features on the constructs [105, 106]. Electrospinning is a powerful tool for creating fibers with nanometer sizes. Yarns made from a bundle of aligned fibers can be created using electrospinning and can be intertwined to form braided scaffolds [105]. It has been shown that the mechanical properties of such constructs mimic the mechanical behavior of native tissue and also can enhance the cellular activity when seeded with hMSCs [105]. Moreover, such scaffolds have been modified with antibacterial biomaterials such as chitosan and used as suturing thread that were bacterial resistance [104, 107](Figure 6).

Due to their flexibility and ability to maintain dimensional stability as well as improved radial compressive strength, braided constructs are ideal scaffolds for engineering nerve conduits [96, 108]. A biodegradable multilayer braided PLA fiber-reinforced conduit has been fabricated to treat a 10mm nerve gap in the rat sciatic nerve [109]. The results indicated that after 8 weeks implantation the scaffold was well integrated and encapsulated by the surrounding tissue. Recently, a novel tabular PLGA construct, consisting of dense outer tube and porous inner tube, has been developed to guide and support peripheral nerve regeneration [108]. Higher braiding density was used for the outside tube in order to serve as support for the space of the nerve regeneration and provide the required compression performance while the interior scaffold had lower PLGA fiber density to function as the matrix bridge in the nerve regeneration process.

Overall, braided constructs offer enhanced mechanical properties under various loading conditions, good flexibility and structural stability, as well as controlled tissue regeneration. These parameters make them an apt choice for tissue reinforcement, grafts in load-bearing

fixations and wound closure and support. However, a key challenge associated with braided tissue scaffolds is their low porosity, which can limit cellular penetration and proliferation. Nevertheless, strategies that allow for the incorporation of cells into the fibers prior to their assembly can overcome this challenge.

4. Emerging Applications of Biotextiles

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

4.1. Cardiovascular tissue engineering

Cardiovascular diseases such as congestive heart failure, coronary artery diseases, and heart valve dysfunction are responsible for ~17 million deaths per year globally and this number is predicted to reach 23.3 million by 2030 [110]. In the case of heart diseases, due to the lack of self repair and renewal characteristics of the heart, organ transplantation is the only solution. However, there is an unmet demand as the number of donors and patients do not match. Tissue engineering holds a great promise to overcome this health barrier by creating functional organs that can replace the injured organ. The fabrication of functional cardiac tissues using current tissue engineering techniques faces key challenges including the ability to i) mimic the cardiac-like molecular composition, structure, electrochemical, and mechanical properties of native tissue and ii) effectively vascularize tissues with clinically relevant dimensions [111]. Thus, a new paradigm for the treatment of cardiovascular tissue damage is needed to provide an effective and long-term therapy for most patients.

Textile technologies are powerful tools for producing finely tuned 2D and 3D constructs from natural or synthetic fibers. Textile manufacturing platforms offer unique advantages over existing scaffold fabrication methods (e.g., salt-leaching [3], bioprinting [5, 47] and micropatterning [112]), including fine control over the size, shape, porosity, and mechanical properties of the fabricated constructs [14, 40, 51]. Proper function of myocardial tissue requires anisotropic mechanical properties and directional cellular alignment (Figure 7a–c). The heart is comprised of long, fibrous muscle cells wrapped in collagen sheaths and interwoven with blood vessels [112]. The shape and orientation of muscle cells within the heart tissue are therefore critical to their electrical and mechanical properties. Thus, fibers can be loaded with different cell types such as hMSCs, endothelial cells (ECs), and human cardiomyocytes (hCMs) as well as growth factors and drugs that augment cellular function. These fibers can be then assembled to mimic the microarchitecture of the native tissue.

Currently, there are several FDA approved biotextiles available for the treatment of cardiovascular diseases and disorders. CorCap™ Cardiac Support Device (CSD) from Acorn Cardiovascular, Inc. is a surgical mesh that is implanted around the heart to provide circumferential myocardial wall support and to reduce the wall stress and myocyte stretch.

Vascular grafts such as Gelsoft™ [113] and Gelweave™ [114–116], from VASCUTEK are also being used for the treatment of diseased aortic vessels.

Biofabrication of scaffolds for cardiovascular tissue engineering using textile methods have been demonstrated by several researchers in the past few years. In an interesting study, a knitted mesh made from hyaluronan benzyl ester (Hyaff-11; Fidia Advanced Biopolymers, AbanoTerme, Italy) was used to create a hybrid cardiac construct [41]. The knitted structure was used to improve the mechanical properties of the engineered construct that underwent cyclic mechanical loads during *in vitro* and *in vivo* studies. The hybrid construct exhibited higher tensile strength and stiffness compared to the native myocardium and remodeled in response to cyclic stretches *in vivo* and *in vitro*. Textile techniques have been combined with other biofabrication methods to create scaffolds that better mimic the microstructure and mechanical properties of the native cardiac tissue. For example, a hybrid knitted-electrospun scaffold has been fabricated to recapitulate the anisotropic mechanical properties of the native myocardium [117]. The results showed significant difference between the surface topology and mechanical properties of the hybrid scaffold and the electrospun construct. The hybrid scaffold contained macroscopic patterns, which assisted cellular alignment, elongation and cardiac-like organization [117].

With the increasing rate of valvular dysfunction, utilization of textile approaches for biofabrication of scaffolds for heart valve engineering has attracted much attention in the past few years. In this context, biotextiles have been mostly used as a reinforcing skeleton for the scaffold. It has been shown that knitted scaffolds developed for tissue engineering of aortic valves had superior resistance against physiological flows compared to their electrospun counterparts [118, 119]. Moreover, knitted scaffolds with micron size pores showed higher cellular infiltration in comparison to electrospun structures [118].

4.2. Musculoskeletal tissue engineering

Musculoskeletal diseases caused by trauma, inflammation, or genetic disorders have a high prevalence. Severe long-term pain and mobility restriction impair the welfare and quality of life of patients with musculoskeletal disease. Current treatments often include the management of symptoms or temporary replacement of the impaired tissue with inert materials. Indeed, tissue engineering is an alternative approach that enables creating functional tissues for organ replacement.

The majority of studies in this area have been focused on the development of engineered ligament and tendon. Braided and knitted constructs have been used alone [105, 120] as scaffolds or reinforcing structures for scaffolds made from other polymers such as collagen [82, 85] or silk [84]. In a notable study, electrospun fibers were braided seeded with hMSCs to engineer a tendon-like construct [105]. Results have shown that using nanofibers improved the mechanical strength of the construct and enhanced the cellular function by mimicking the dimensionality of collagen fibrils in native tissue [105]. In another study, it was shown that a woven scaffold made from collagen threads with densely compacted and anisotropically aligned substrate textures stimulated tenogenesis topographically [120]. Therefore, such scaffolds can serve as a substrate for functional repair of ligaments and tendons.

4.3. Wound dressing

Wound is defined as a break or cut in any tissue [121]. Management of skin wounds is one of the earliest medical activities of humans. During the past centuries, aligned with advances in biological and material sciences, more effective technologies have emerged for treating various wound types [122]. New developments have also been boosted by the market size of wound management products ($28.7 billion in 2013) [123]. Ideal wound dressings should: i) permeate oxygen; ii) keep the area moist; iii) remove excess exudates; iv) be biocompatible and non-allergenic; v) inhibit micro-organisms growth; vi) provide appropriate stimulation and growth factors during different stages of wound healing; vii) possess suitable mechanical properties that prevent any potential discomfort while maintaining conformal contact between the dressing and the wound.

Textile systems have been widely used as wound dressings since they possess oxygen permeable porous microstructure with the ability to wick exudates. The scalability of textile fabrics also adds to their robustness for use in wounds with different sizes. The ability of textile systems for tuning the mechanical properties of the generated constructs is another key advantage that allows fabrication of dressings that are elastic and flexible to maintain their contact with the wound. Traditionally, textile dressing in the form of medical gauze and bandage has been fabricated from a range of natural and synthetic materials including cotton, silk, PGA, polyester, and polyurethane [124]. The conventional dressing can provide support to the wound during the healing process and are air and exudates permeable. Textile-based wound dressings can offer hemostatic properties by incorporation of proper reagents or applying mechanical force to physically close the wound [125, 126].

These conventional textile systems, however, cannot maintain moisture in the wound area and fail to inhibit bacterial growth [124]. To solve the later challenge, fibers or fabrics have been coated with antibacterial reagents such as silver and honey [123, 127, 128]. However, the generation of wet textile-based wound dressings has been impossible due to the insufficient mechanical strength of hydrogels and hydrocolloidic fibers. Recent advancements in fabrication of hydrogel fabrics [15] (Figure 5) and the introduction of CLFs [16] (Figure 3) have paved the path for creation of wet fabrics that can potentially be used as wound dressings. In a study, Knill *et al.* fabricated bi-layer alginate and chitosan hydrogel fibers with antibacterial properties and randomly assembled them as a wet wound dressing (Figure 8) [129]. Another important characteristic of wet wound dressings is their ability for drug and growth factor delivery to the wound area to promote the healing process [130]. Recent advancements of textile-based electronics can also potentially lead to the development of dressings for sensing and stimulating the wound area to improve the healing rate. Thus, development of scalable techniques for generation of mechanically robust wet fabrics could potentially have an enormous impact on the advancement of wound management systems.

Biotextile, with a long history of being used as dressings for wound management, are promising substrates for advanced wound healing applications. Biotextiles combined with recent advances in biomaterials, drug delivery and fiber-based electronics hold a great promise for developing smart fabrics with the capability of monitoring the wound condition and performing suitable treatments.

4.4. Wearable Electronics

Recent advances in micro and nanofabrication technologies combined with progresses in the area of polymeric sciences have enabled the development of a new class of electrical systems that are flexible, elastic, and even biodegradable [18]. One area that has received noticeable attention for the fabrication of such systems is textile-based approach, specifically due to the tunable physical characteristics of the generated fabrics and their hierarchical nature [131]. This new class of electronics are wearable and similar to regular fabrics can form conformal contact with skin [132, 133]. In addition, electrically-enabled fabrics have been made from polymeric materials that are implantable as sensors or actuators [133]. In general, electrically-enabled fabrics have been employed for various applications including flexible circuits [134], radio-frequency identification tags [135], wearable energy harvesting systems [136] and tissue engineering scaffolds [137].

An important factor in design of fiber-based electronics is the selection and introduction of the conductive materials into the system. The selected material should possess electrical conductivity and mechanical properties that suit specific applications. For example, the conductive material should be flexible to allow its incorporation into the fabric and should maintain its normal function once worn or implanted [133]. The conductive material can be selected from metallic fibers, metallic particles and nanowires, carbon nanotubes, graphene, reduced graphene oxide, or conductive polymers [133].

Conductive fibers can either be used directly or in combination with non-conductive threads for making wearable fabrics [138, 139]. In addition, conductive fibers or yarns can be created by coating a core fiber with a layer of conductive ink or polymer [140, 141]. These fibers or yarns are then interweaved or knitted into a fabric or can be added through an embroidery process to create conductive patterns [138, 142]. It is also possible to render a regular fabric electrically conductive by simply coating it with or dipping it into a solution containing nanoparticles or nanowires [143]. Conventional patterning methods including screen printing by means of a shadow mask, applying the ink using brush, spin coating, or spraying can also be used to create conductive patterns on textiles. Textile fabrics are also compatible with inkjet and contact printing, which possess a higher resolution in comparison to screen printing. Our group has recently introduced a biodegradable nanofibrous mat of PGS-PCL as a suitable substrate for flexible and elastic sensors (Figure 9c) [18]. Temperature and strain sensors were screen printed on top of the substrate and it was shown that the electrical functionality of the created patterns was maintained over a range of tensile strains and radii of curvature.

Biodegradable fabrics with embedded electronics have several applications in the field of tissue engineering and regenerative medicine. For example, it is now well documented that electrical stimulation can affect cellular behavior of muscles and neurons and thus can be used to control their alignment and function [144, 145]. In addition, it has been demonstrated that proper electrical stimulation promostes synchronize the beating of cardiomyocytes cultures, which is an important step towards engineering functional cardiac tissues [146]. These observations combined with tunable mechanical properties and biomimetic microarchitecture offerred by textiles have motivated researchers to design electrically-enabled tissue engineering scaffolds. In a notable study, a network of nanowires

were fabricated and used to create tissue engineering scaffolds for both stimulating cellular cultures and sensing their activity *in situ* (Figure 9d) [137]. In particular, the scaffolds enabled monitoring the local electrical activity of cardiomyocytes and neurons and their response to drugs.

Overall, the integration of sensors with textiles is an exciting approach for developing wearable devices for continuous monitoring of the human body health. Electrically-enabled fabrics combine the physical characteristics of textiles (tunable mechanical properties and high porosity) with advanced electronics and sensors to create multifunctional scaffolds for cardiac and neural tissue engineering. In addition, by utilization of resorbable metals such as Mg and Zn, fully degradable systems can be realized and implanted without a second retrieval surgery.

5. Challenges and Future Prospects

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

Despite numerous advantages offered by textile technology, there are still several challenges that have to be addressed to use this technology up to its full potential. The main obstacle for the use of biotextiles for tissue engineering and regenerative medicine is combining state-of-the-art textile machinery, novel biomaterials, and biological advances to create tissues and organs automatically. Although fibers made from synthetic materials are mechanically strong and can be assembled into complex structures using textile approaches, the harsh manufacturing process hampers the ability to encapsulate cells inside them. Current methods for creating cell-laden fibers yield to the fabrication of fibers that are not mechanically strong to withstand the mechanical loads exerted during the manufacturing process. Such challenge has been recently addressed by developing composite living fibers (CLFs) that were composed of a mechanically strong core material coated with a cell-laden hydrogel layer. However, the surface of CLFs is also slippery which can make their assembly challenging. Thus, more advanced fiber fabrication techniques should be developed to allow the fabrication of cell-laden fibers with properties comparable to the currently used threads. Accordingly, it is expected that the field of textile tissue engineering will significantly move towards this direction. To allow assembly of cell-laden fibers, new textile machines that can control humidity, oxygen, and CO_2 level, create a sterile environment, and facilitate nutrient access to cells within the fibers and generated fabrics is required.

While great advancements have been made in the field of biotextiles, implantable fabrics are in use for limited applications. The main challenge is the inability to capture the in vivo mechano-biological properties of different organs and tissues. This challenge can be addressed by creating different fibers from advanced biomaterials with tunable physico-chemical properties capable of delivering growth factors and chemokines.

Another potential direction for the use of textile-based tissues is creating *in vitro* disease models and drug testing platforms. By assembly of cell-laden fibers, different cells can be interfaced to facilitate the cross-talk between multiple cell types within a tissue. These advanced living fabrics can be combined with current organ-on-a-chip platforms. Flexible and wearable electronics and sensors are other areas that have been benefitted from advances in biotextile engineering. It is expected that the field will grow towards engineering implantable and biodegradable sensors and devices fabricated from textiles. One area that can likewise see a noticeable attention is the incorporation of electronics within tissue scaffolds for monitoring cellular activity or stimulating them.

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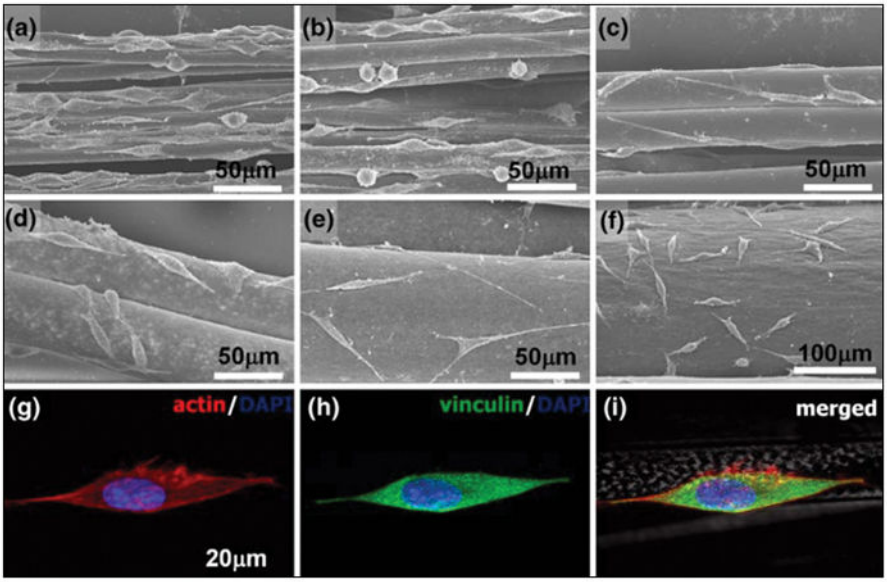

Figure 1.

Controlling the orientation of cells on microfibers by changing the fiber diameter. (a–f) L929 fibroblast morphology on PLGA fiber with diameters ranging from 10 μm to 242 μm. (g–i) Immunostained cells oriented along 30 μm diameter fiber direction. Reprinted with permission from Springer (2009) [31].

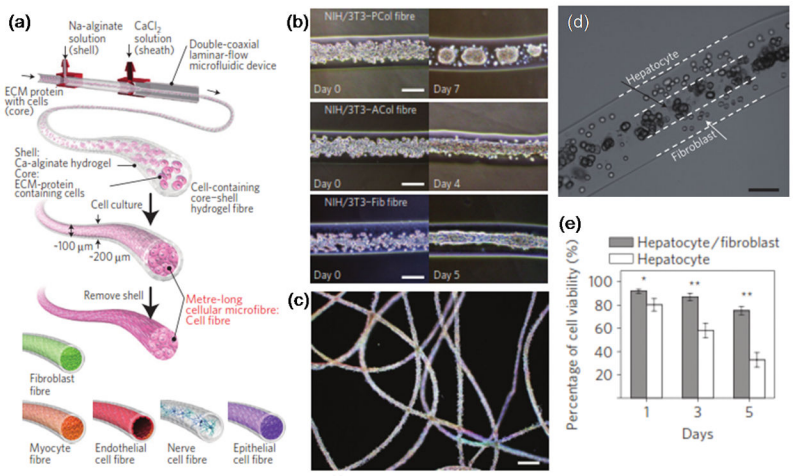

Figure 2.

Manufacturing of cell-laden hydrogel microfibers using double co-axial flow microfluidics. (a) Cell-laden ECM proteins are entrapped in a calcium-alginate shell to form various types of functional fibers. (b) Cellular growth in ECM-based proteins. (c) Long cell fibers after 4 days of culture and removal of the alginate layer. (d) Co-culture of hepatocytes and fibroblasts on a single multilayer hydrogel microfiber. (e) Comparison of cellular viability in co-culture and single culture. Reprinted with permission from Nature Publishing (2011) and (2013) [15, 48].

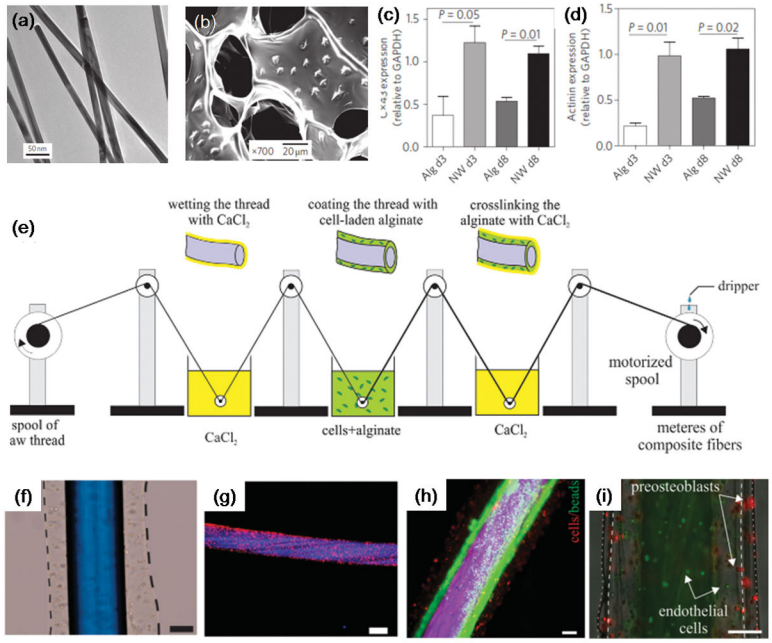

Figure 3.

Composite materials showing superior mechanical and electrical characteristics. Incorporation of gold nanowires (a) within alginate matrix (d) improved the electrical conductivity the composite material and promoted cardiomyocyte function. Expression of (c) connexin 43 and (d) actinin for alginate (Alg) and composite alginate-nanowire (NW) on day 3 and day 8. (e) Fabrication of composite living fibers made from a mechanically strong core material and a hydrogel layer. Encapsulation of cells on a (f) Non-absorbable monofilament suture, (g) Catgut suture. (h, i) Multilayers of cells and biomolecules (represented by fluorescently-labeled beads). Reprinted with permission from Nature Publishing 2011 and John Wiley and Sons (2014) [16, 71].

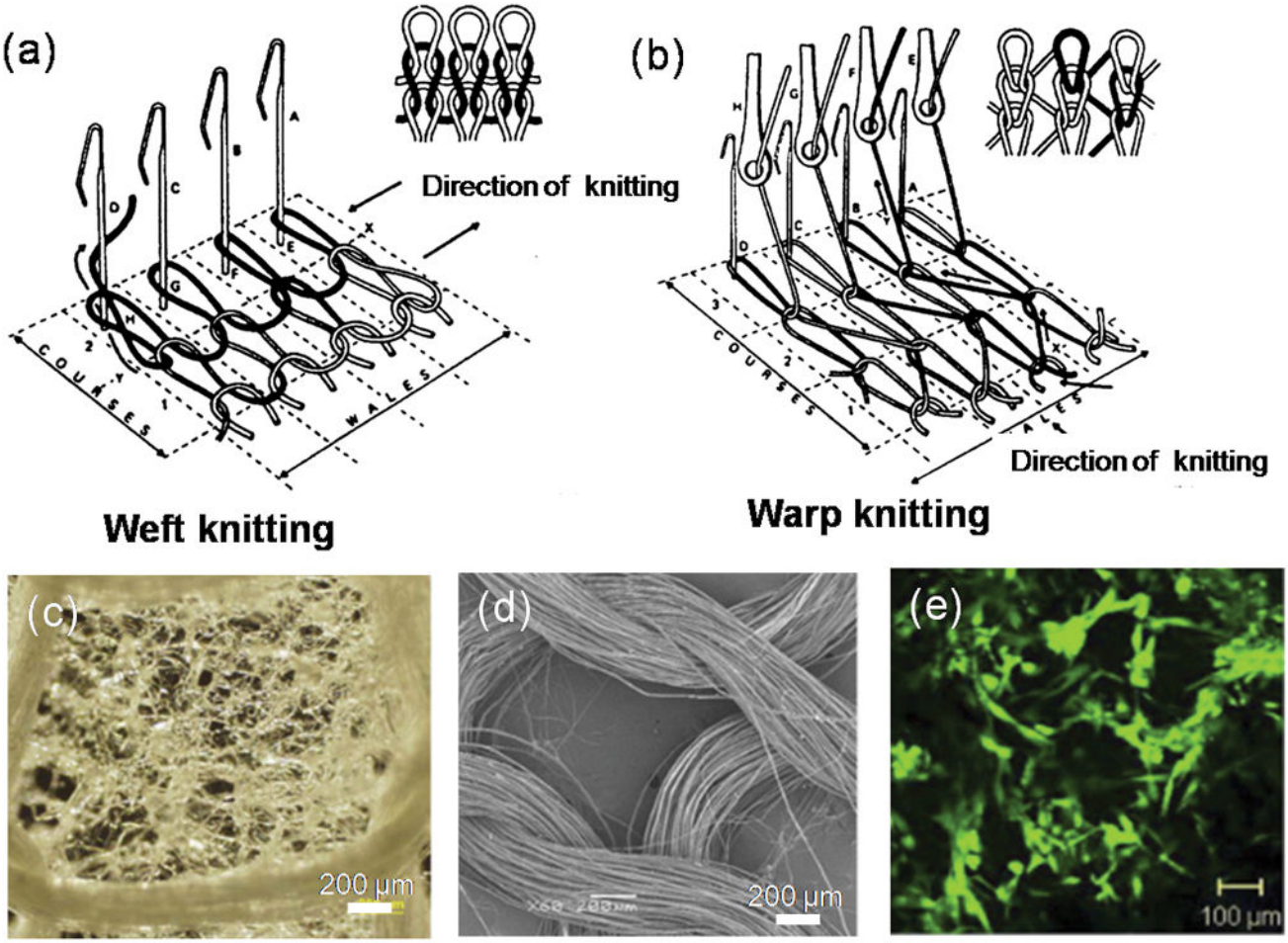

Figure 4.

Fabrication of knitted fabrics and their tissue engineering applications. (a,b) Schematic diagrams of various knitting processes and stitches; (a) Weft and (b) warp knitting. (c) Combined knitted silk scaffold and collagen sponge. (d) Knitted silk scaffold. (e) hMSCs grown on the combined knitted scaffold with high viability and proliferation rate. Reprinted with permission from Elsevier (2000) and (2008) [78, 79].

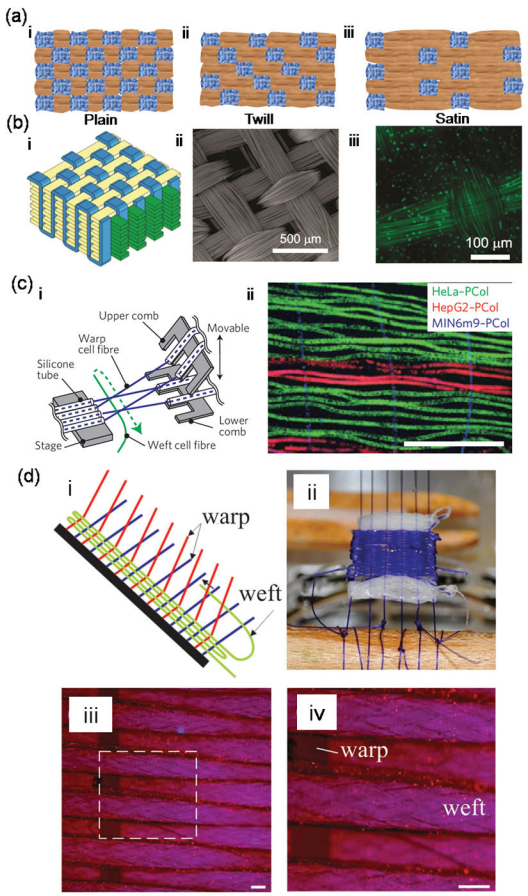

Figure 5.

Woven fabrics and their use in tissue engineering. (a) Various common weaves including plain (i), twill (ii), and satin (iii). (b) 3D woven scaffold generated with interlocking several layers for cartilage tissue engineering, schematic (i), a representative SEM image of woven PGA scaffolds (ii), a typical scaffold covered with condrocyte-laden agarose (iii). (c) Weaving hydrogel fabrics using a microweaving loom (i), the loom was employed to create a patterned hydrogel fabric.(d) Assembly of CLFs using an off the shelf weaving loom (i,ii), representative micrograph demonstrating a typical fabricated cell-laden fabric (iii,iv). Reprinted with permission from Nature Publishing (2007) [14] and (2013) [15] and John Wiley and Sons (2014) [16].

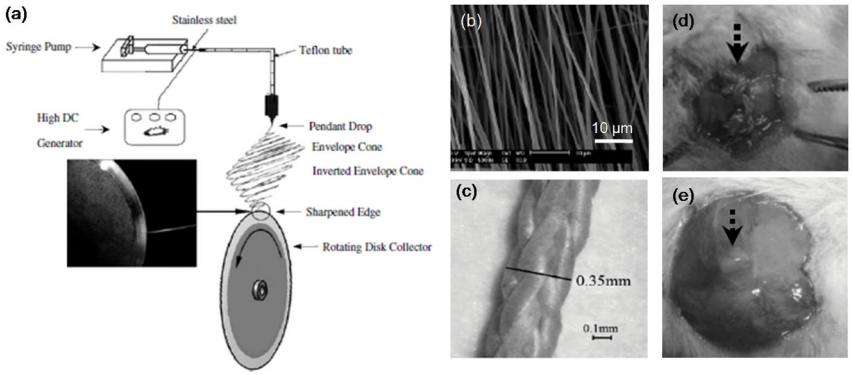

Figure 6.

Fabrication of braided constructs using electrospun nanofibers. (a) Schematic showing the process of fabricating aligned electrospun fibers. (b) Aligned electrospun fibers. (c) Braid the aligned multifilament fibers into a scaffold. Braided construct implanted in a rat forelimb after 1 day (d) and 28 days (e) showing smooth healing. Reprinted with permission from John Wiley and Son's (2010) [104].

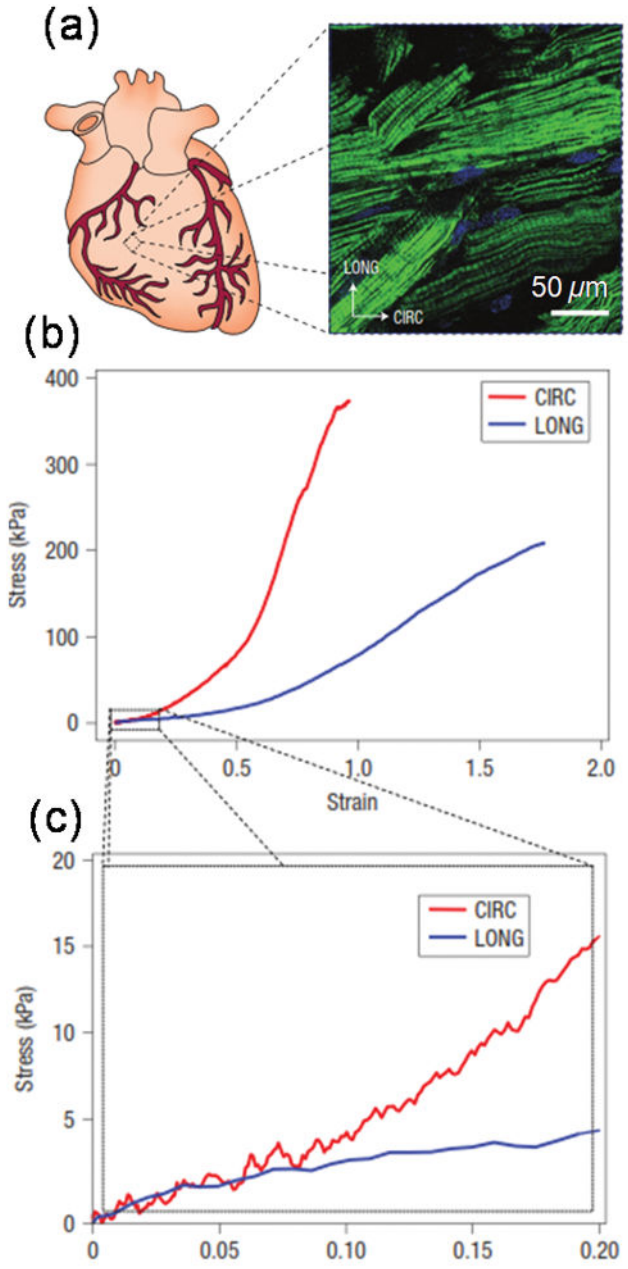

Figure 7.

Textile-based methods for engineering of cardiac tissues. (a) Microstructure of cardiac muscle with preferentially oriented cardiac muscle fibers. (b–c) Anisotropic mechanical properties of right ventricular myocardium showing the directionality of uniaxial tensile strength. Reprinted with permission from Nature (2008) [112].

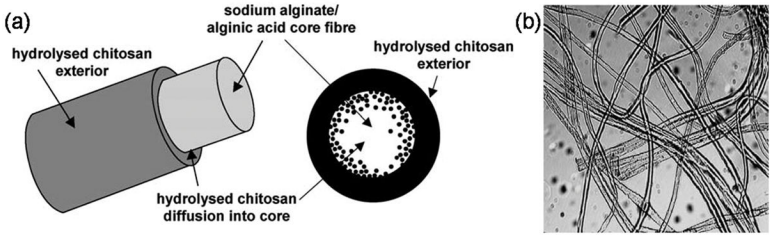

Figure 8.

Bi-layer hydrogel fibers for antibacterial wound dressing (a) Schematic of the fiber microarchitecture. (b) A representative micrograph of fabricated alginate-chitosan hydrogel fibers. Reprinted with permission from Elsevier (2004) [129].

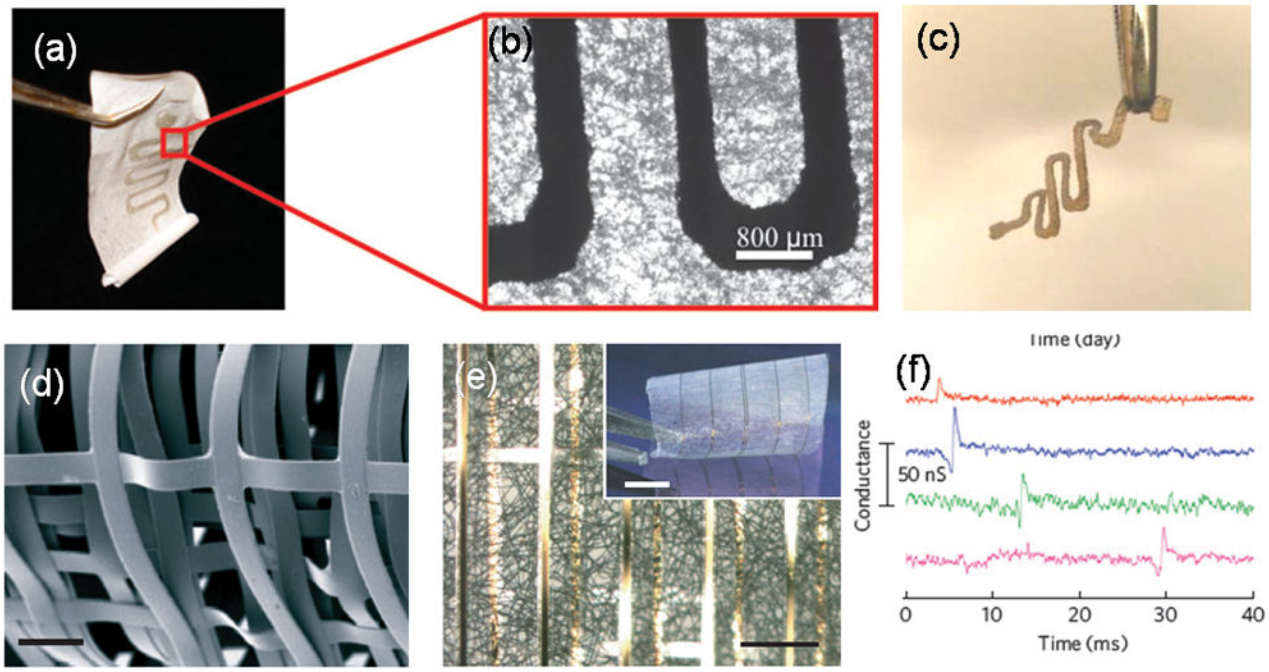

Figure 9.

Engineering fiber-based implantable electronics. (a) A typical PGS-PCL nanofibrous substrate with a conductive silver pattern. (b) and micrograph showing the microstructure of the sheet and the patterned conductive lines. (c) Image of the conductive microstructure after complete degradation of the substrate [13]. (d) SEM image of electrical system formed from a network of nanowires engineered for creating electrically enabled scaffolds. (e) Micrograph showing a hybrid multilayered PLGA scaffold. The inset shows the photograph of a typical hybrid scaffold. Scale bars, 200 μm and 5mm (inset). (f) Electrical measurement of extracellular field potentials using the hybrid mesh [88]. Reprinted with permission from John Wiley and Son's (2014) [18] and Nature Publishing Group (2012)[137].

Table 1

Summary of different bioactive fibers and their advantages and disadvantages.

Type of biofibers	Advantages	Disadvantages
Synthetic	• High mechanical strength • Tunable mechanical properties • Controllable surface morphology	• Harsh fabrication process for cells • Inability to encapsulate cells • Lack of binding sites for cells on these fibers' surface
Hydrogel	• Cell-nurturing environment • Ability to encapsulate cells • Mild fabrication process for cells • Ability to incorporate cell binding ligands that promote cellular function	• Low mechanical strength • Difficult to handle
Natural	• Biocompatibility • Biodegradability to harmless products	• Complex purification process • Immunogenicity • Pathogen transmission
Composite	• Ability to combine and tune different physical properties • Ability to incorporate cells within the fiber	• Difference in the degradation rate of components • Delamination of the phases

Table 2

Summary of textile methods for fabricating tissue constructs and their advantages and disadvantages.

Textile method	Advantages	Disadvantages
Knitting	• High flexibility • Adjusting properties in different directions is difficult	• Ability to create 3D complex structures using CAD systems
Weaving	• Ability to create constructs with anisotropic properties • Process is less mechanically harsh compared to knitting	• Less flexibility compared to knitting • Low porosity
Braiding	• Excellent flexibility and structural stability • Good for lead-bearing tissues	• Low porosity • 1D structure