



Review

Electrospinning versus microfluidic spinning of functional fibers for biomedical applications

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ABSTRACT

Micro- or nanofiber-based materials have extensive applications in biomedical fields due to their capability to mimic many aspects of physiological microenvironment *in vivo*. Fabricating micro- or nanofibers using biocompatible and biodegradable materials is becoming of great interest in the area of biomaterials and tissue engineering. Among the various technologies, electrospinning and microfluidic spinning are the two promising approaches to produce fibers at micro- and nano-scale. Choosing an appropriate spinning method is critical important for a specific application. Although some review papers on each spinning method have been published, a review comparing these two methods has not been reported yet. In this review, we present an overview of the two spinning methods including the spinning principle, their unique features and materials selections. Several applications of fibers spun by both methods, especially in tissue engineering, organ function regeneration and drug delivery are introduced. The current challenges, future directions and potential applications of these approaches are discussed as well.

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1. Introduction

Nature has provided inspiration for a variety of engineering projects. The connective tissues in our bodies, for example, have inspired investigators to develop new methods for producing micro- or nanofibers. Generally, connective tissues consisting of amorphous gel-like non-fiber ground substances, fibers, and cells are essential for living organisms. Diverse fibers, such as collagen and elastin, play a key role in forming and maintaining the shape of these tissues. Inspired by such tissues in living creatures, many scientists have started to engineer tissues in the laboratory using a variety of highly porous scaffolds to promote cell adhesion and proliferation, e.g., sponge-like sheets, foams, highly complex structures, and fibers [1–4]. Among these porous scaffolds, the scaffold consisting of micro- or nanofibers offers the advantages of

being able to control the pore sizes precisely and the orientation of the porous structure and can provide cells with microenvironments that mimic the physiological milieu. To date, various spinning methods have been developed to produce micro- or nanoscale fibers and the most commonly used methods among them are electrospinning and microfluidic spinning. These methods can also control the shape, surface features, and chemical composition of a single fiber. The 2D and 3D scaffolds consisting of these fibers can provide chemical and physical cues to regulate cellular behaviors including cell adhesion, proliferation, extracellular matrix (ECM) production, morphogenesis, and differentiation.

Electrospinning is one of the two main electrohydrodynamic atomization techniques, the other main electrohydrodynamic atomization technique is electrospraying, a powerful technique for monodisperse particles preparation [5]. Electrospinning is a typically used dry spinning process, which was first developed over seventy years ago [6]. It produces fine polymer fibrous mats composed of fibers whose diameters range from several microns down to 100 nm or less. The basic difference between electrospinning and electrospraying lies in the concentration and viscosity of the polymer solution. Polymer solution with low viscosity is the prerequisite for electrospraying, in contrast, the high viscosity is the

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Abbreviations	
<i>Solvent</i>	
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
THF	tetrahydrofuran
DCM	dichloromethane
DMF	N, N-dimethylformamide
TFE	2,2,2-trifluoroethanol
TFA	Trifluoroacetic acid
DMA	Dimethylacetamide
DMSO	Dimethyl sulfoxide
DMAC	Dimethyl acetamide
LiCl	Lithium chloride
CPSA	Camphorsulfonic acid
IPA	isopropyl alcohol
<i>Polymer</i>	
PVA	Poly(vinyl alcohol)
PCL	Polycaprolactone
PEUU	Poly(ester urethane)urea elastomer
PLA	poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PAN-MA	Poly(acrylonitrile-co-methylacrylate)
PCE	Poly(ϵ -caprolactone)-poly(ethylene glycol)
PGS	Poly(glycerol sebacate)
MET	Metronidazole benzoate
PCU	Polycarbonate-urethane
NIPAm	N-Isopropylacrylamide
pNIPAm	Poly(N-isopropylacrylamide)
PDMS	Polydimethylsiloxane
PVP	Polyvinyl pyrrolidone
PU	Polyurethane
PHBV	Poly(3-hydroxybutyrateco-3-hydroxyvalerate)
PMMA	Poly(methyl methacrylate)
PEGdma	Poly(ethylene glycol) dimethacrylate
PLLACL	Poly(L-lactic acid)-co-poly(ϵ -caprolactone)
PEO	Polyethylene oxide
PES	Polyethersulfone
PS	Polystyrene
PGA	Poly(glycolic acid)
PDS	Polydioxanone
PANI	Polyaniline
PPC	Poly(propyl carbonate)
PCHC	Poly(cyclohexyl carbonate)
PCL-PEG-PCL, PCEC	Poly(ϵ -caprolactone)-poly(ethylene glycol)-poly(ϵ -caprolactone)
PCE	Poly(ϵ -caprolactone)-poly(ethylene glycol)
PPHOS	Poly[(glycine ethyl glycinate) ₁ (phenylphenoxy) ₁ phosphazene]
PNmPh	polyphosphazene
PEGDA	poly(ethylene glycol) diacrylate
PEGDMA	Poly(ethylene glycol) dimethacrylates
4-HBA	4-hydroxybutyl acrylate
PBI	Polybenzimidazole
PMMA	Poly(methylmethacrylate)
PPDO-co-PCL- <i>b</i> -PEG- <i>b</i> - PPDO-co-PCL	Poly(<i>p</i> -dioxanone- <i>co</i> -caprolactone)- <i>block</i> -poly(ethylene oxide)- <i>block</i> -poly(<i>p</i> -dioxanone- <i>co</i> -caprolactone)
PGA	Propylene glycol alginate
PLL	Polylysine
DA	Diacetylene
PDA	Polydiacetylene
GelMA	gelatin methacrylamide
Gtn-HPA	gelatin-hydroxyphenylpropionic acid
Alg-Ph	alginate-phenolic hydroxyl
Gel-Ph	gelatin-phenolic hydroxyl
PBI	poly(2,2'-(<i>m</i> -phenylene)-5,5'-bibenzimidazole)
PAN	polyacrylonitrile
PSF	polysulfone
PS	polystyrene
PUA	polyurethane acrylate
PETMP	Pentaerythritol tetrakis (3-mercaptopropionate)
DA.	diacetylene

prerequisite for electrospinning. In electrospraying, the electrified polymer jet is broken into small droplets due to the low viscosity, and these droplets further solidify into particles through rapid evaporation [5]. In electrospinning, the viscous polymer solution forms a hemisphere at the tip of the needle due to surface tension, and a charged polymer jet is further formed. This jet solution gradually concentrates and solidifies into fibers after a series of physical process including “bending instability” and “whipping motion” [5]. Electrospinning requires the high DC voltage in the range of several tens of kVs for the spinning. A variety of natural and synthetic polymers were used as materials for the tissue engineering application. By the recent progress of electrospinning technology, fibers with diverse shapes, such as tubular shapes, and multiple-fiber structures have been fabricated.

Microfluidics is a technology to enable the precise manipulation of fluid within microscale channels, which has shown considerable promise for application in biomedicine [7]. After PDMS was firstly introduced into the microfluidics field in 1998, more complex microfluidic devices were able to be fabricated through soft lithography method, which greatly accelerates the development of the microfluidics technology [7]. Recently, microfluidics technologies have shown the potential to solve problems that have not yet

been solved by traditional macroscale methods, particularly in the diagnostic field [7]. Microfluidics-based diagnostics devices could be attractive candidates to replace traditional diagnostics approaches because they are simpler, faster and more sensitive than traditional methods [7]. Besides applications in diagnostics, microfluidics is also a powerful tool to fabricate structural materials like fibers. Microfluidic spinning, as a typically used wet spinning process, was developed about 10 years ago [8,9]. Progress in microfluidic technology has enhanced the ability to control a very small quantity of liquid, resulting in the development of new chemical assays and the production of large quantities of microstructures, such as particles, fibers and tubes, without use of complicated devices and facilities. It is especially notable that microfluidic spinning can continuously produce microfibers with a uniform diameter and spatiotemporal control. Although fibers spun by both methods have attracted extensive attention and used widely in tissue engineering and drug delivery, each method has its unique features. To date, many review papers for each spinning method have been published; however, a review comparing these methods has not been reported to the best of our knowledge [10–25].

In this review, we present an overview of both spinning

methods covering the principle behind each spinning method, their unique features and the materials that can be used for their applications, especially in tissue engineering, organ function regeneration and drug delivery. Although these two spinning methods are based on different principles, they can both generate diverse fibrous structures, especially as the technology progresses. We also describe future directions and further applications of these technologies.

2. Comparison of the electrospinning and microfluidic spinning methodologies

Although both spinning methods can produce microscale and nanoscale fibers, the spinning principles, materials and environments are different. Here, we compared the major features of each method item by item, as listed in [Table 1](#). The materials, the fabrication processes, and the fibers' morphologies are especially important for the applications. Therefore, in this section, we provide an extensive description of these particular features as follows:

2.1. Principles underlying electrospinning and microfluidic spinning

Electrospinning is a fabrication process in which fine polymeric fibers are produced from a liquid using electrostatic force. A schematic diagram of the electrospinning process is shown in [Fig. 1A](#). The system for this type of spinning normally consists of three components: a supplier of high voltage, a needle connected to a syringe, and a metal collector. The voltage supplier introduces a high electrical potential between the needle and the grounded metal collector. Initially, the polymer solution forms a hemisphere at the tip of the needle due to surface tension. As electrical potential is applied, the hemispherical surface of the polymer solution elongates to form a Taylor cone. A further increase of the electrical potential overcomes the surface tension and causes the formation of polymer jet towards the metal collector. This jet solution gradually concentrates with the evaporation of solvent and then solidifies before reaching the collector. The charged polymer jet could eventually be collected on either a stationary collector to form a randomly oriented nanofiber mat or a dynamic collector to form a highly aligned nanofiber mat. Although the concept of electrospinning is simple, the system is very sensitive to a number of parameters including those of the solution used and the process deployed, as well as the specific ambient conditions (relative humidity and temperature, etc.). Therefore, reproducible fabrication of electrospun fibers with a finely controlled diameter remains challenging.

In contrast, microfluidic spinning involves the science of micro-scale fluid dynamics, as shown in [Fig. 1B](#). Fluid flowing in a microchannel behaves differently from bulk fluid due to differences on the surface tension and energy dissipation, as well as fluidic resistance. Based on this principle, a 3D coaxial flow consisting of sample and sheath flows can be created by employing a specially designed microchannel. By solidifying the coaxially flowing liquid using UV light, ionic or chemical crosslinking and solvent exchange, solidified fibers can be produced. 3D sheath flow surrounding the sample flow functions very well as a lubricant to prevent the direct contact between the channel wall and the sample, and hence prevents the microchannel from becoming clogged.

2.2. Materials

The basic materials for electrospinning are polymers and solvents. In theory, as long as a suitable solvent can be found, most natural and synthetic polymers are able to be electrospun into

fibers. To date, more than 200 polymers have been successfully electrospun [[26,27](#)]. However, the characteristics of the polymers, including their mechanical properties, degradation rates, and biocompatibility, should be considered when the resulting as-spun fibers are used for tissue engineering. Both the natural and synthetic polymers most frequently used for tissue engineering are summarized in [Fig. 2](#) and [Table S1](#). Many biocompatible and biodegradable synthetic polymers, such as PCL, PLA, PLGA, PVA, PEO, and PLLACL, have been directly electrospun into nanofibers for tissue engineering applications. The degradation behaviors and mechanical properties of the scaffolds are critical issues, and in general any single polymer does not have both the degradation and mechanical properties necessary for successful spinning. Therefore, synthetic polymers blended with other materials are commonly utilized. Several natural polymers have been electrospun into scaffolds and used for tissue engineering, including natural proteins (e.g., collagen, gelatin, fibrinogen, elastin, and silk) and natural carbohydrates (e.g., chitosan, dextran, alginate, hyaluronic acid, chondroitin sulfate, and chitin) ([Fig. 2](#) and [Table S1](#)). Although the electrospun natural polymer nanofibers can provide more of an ECM-like environment than the synthetic polymers, their faster degradation limits their efficacy in scaffold applications. In addition, electrospinning of pure natural polymers is generally difficult. For example, electrospinning of chitosan, a widely explored polysaccharide, is very challenging due to its high charge density and plentiful hydrogen bonding. To the best of our knowledge, alginate, another common polysaccharide, has not been electrospun by itself until now due to its high viscosity and intermolecular repulsion between anionic groups [[28](#)]. Therefore, natural polymers are always co-electrospun with synthetic polymers such as PEO and PCL. The composite electrospun nanofibers composed of natural and synthetic polymers express both the beneficial biological properties of natural polymers and the physicochemical/mechanical properties of the synthetic polymers. However, the bioactive characteristics of the natural polymer may be partially changed when combined with synthetic polymer.

Selecting a suitable solvent for electrospinning is another critical aspect of the work. The solvent should not only dissolve the polymer to a sufficiently high concentration before electrospinning, but also should evaporate before the polymer jet reaches the collector. Although rapid evaporation of the solvent is needed, the solvent volatility should be appropriate, since solvents that are too volatile will clog the needle. Furthermore, solvents strongly influence the viscosity, surface tension and conductivity of the polymer dispersion, which should be considered before electrospinning. Obviously, water is the most desirable solvent; however, most synthetic polymers are relatively hydrophobic and hence do not easily dissolve in water. Organic solvents, such as HFIP, DCM, acetone, TFE, TFA, ethanol, chloroform, and DMF, are the main solvents used for electrospinning. Some polymer blends require specific solvent mixtures such as methanol/chloroform, THF/DMF, and formic acid/chloroform/acetone ([Table S1](#)). The main disadvantage of organic solvents is their toxicity. In contrast to microfluidic spinning, in which the materials are usually cell-friendly, electrospinning commonly utilizes highly cytotoxic organic solvents, which present a great hurdle for the applications of electrospun fibers in biomedical engineering. The involvement of organic solvents prevented electrospinning from being applied to the fabrication of cell-laden or sensitive molecule-laden fibers. Moreover, solvent residue on the fiber surface may render the fibers cytotoxic, thereby limiting their development in biomedical applications such as tissue scaffolds and wound-healing patches. In addition, denaturation of natural proteins is the most intractable problem during electrospinning due to the extreme conditions of the processing environment and the organic solvents used. About 45% of the triple

helical structure of collagen was shown to be lost during electrospinning [29].

Compared to electrospinning, microfluidic spinning is more suitable for natural polymers than electrospinning. Microfluidic spinning affords advantages such as a mild spinning environment, the ability to spin natural polymers without using synthetic polymers as aids and a toxic solvent, uniformity in the size and shape of the resulting fibers without the formation of droplets, and the ability to handle single fiber. Most natural polymers that can be spun into fibers using microfluidic spinning are fabricated in an aqueous environment, hence avoiding denaturalization during the fabrication process. Furthermore, sensitive materials used for cell adhesion and culture are generally left undamaged after microfluidic spinning. By using microfluidic spinning, diverse hydrogel-based microfibers have been created, apparently resulting from the coaxial laminar flow of sample solution (pre-polymer) and sheath fluids (crosslinking agent). Since most hydrogels are biocompatible, biodegradable, and mechanically processable, they are commonly used as scaffolds [30]. Both natural polymers (e.g., alginate, collagen, and chitosan) and synthetic polymers (e.g., PU, 4-HBA, PEG-DA, amphiphilic triblock (PPDO-co-PCL-b-PEG-b-PPDO-co-PCL), and PUA) have been transformed into solids using diverse crosslinking methods (Fig. 1B) [21]. In contrast to electrospinning, however, microfluidic spinning requires the proper selection of materials to serve as the sample and sheath fluid pair in order to achieve successful *in situ* crosslinking. Also, the mechanical properties and pore sizes of the products were determined by the concentration of pre-polymer and their cross-linkers [31]. Several crosslinking methods that are employed for microfluidic spinning can be categorized into four groups: (1) photopolymerization, (2) ionic crosslinking, (3) solvent exchange, and (4) chemical crosslinking (Fig. 1B). For photopolymerization, UV light (generally 365 nm) is irradiated onto the flow stream. Photopolymerizable polymers such as PEG-DA [9,32–37] or 4-HBA [9,34,38–40] are generally used as a backbone material, and photo-initiators are added to induce the photopolymerization. Although this method is simple and stable, its application in tissue engineering is limited by the potential harm that UV radiation may cause to cells, and the materials that are not biodegradable. Both chemical and ionic crosslinking are popularly used to prepare various biodegradable and biocompatible microfibers through the formation of covalent or noncovalent bonds between the polymer chains and cross-linkers. The typical polymers used are alginate [41–65], PLGA [66–68], chitosan [69–71], gelatin–hydroxyphenylpropionic acid (Gtn–HPA) [72,73], and vanadium pentoxide (V_2O_5) [74]. In addition, solvent exchange methods involving diffusion-based mass exchange between a polymer solution and a non-solvent can generate polymerized fibers using amphiphilic triblock copolymer [75].

Of these biomaterials, alginate is the most frequently used in cell-laden fibers because of its simple and rapid gelation process, excellent biocompatibility and biodegradability [76]. Treatment of the fiber surface and the use of alginate-based ECM hydrogel fibers have been reported to improve the adhesion and viability of cells on microfibers. Sakai et al. developed alginate–gelatin-mixed hydrogel fibers treated with oxidized alginate to support cell proliferation and adhesiveness on fibers [77]. Lee et al. fabricated chitosan-alginate fibers using a microfluidic chip since chitosan is one of the most suitable scaffold materials for liver tissue, and showed enhanced adhesion and viability of HepG2 cells on the fibers [78]. Onoe et al. encapsulated various ECM proteins such as collagen, fibrin, or agarose in alginate fibers to provide a suitable microenvironment for the cells and reconstruct fiber-shaped functional tissues to mimic the physiological environment [79]. Silk fibroin fiber was prepared using a PEO solution as the sheath flow, and the

as-spun fibers were collected by using an ethanol bath in which silk fibroins were crosslinked through forming intra- or intermolecular β -sheets [80]. Cell-laden silk fibroin hydrogel fibers were also prepared by mimicking silkworm spinning process [81]. Alginate was used as a sericin-like material to generate stable silk fibroin fibers, and L929 fibroblasts encapsulated in the fibers displayed excellent cell viability compared to those in pure alginate fibers [81].

2.3. Spinning processes for the production of diverse fibers and environments

The advantage of electrospinning fabrication process lies in its simplicity, cost effectiveness, and the possibility for scaled-up fabrication. Usually, electrospinning takes place at room temperature in a dry environment. The spinning needle is the main component of an electrospinning set up. In general, a needle with a single channel is the most popular type. Several modified types of spinning needles, such as coaxial needles and side-by-side needles, have been fabricated for the purpose of producing more diverse nanofibers. Recently, a set of new designs called needleless electrospinning has been developed to produce nanofibers on large scales. Instead of a needle, an open liquid surface is used as a spinneret on which numerous jets are formed. A series of needleless electrospinning spinnerets have been reported so far, including magnetic fields [82], rotating rollers [83], air bubbles [84], metal plates [85], splashing spinnerets [86], rotary cones [87], cylinders [88] and bowel edges [89,90]. Recently, Tamerler et al. designed a needleless spinning system called infusion gyration method which was consisted of rotary aluminum cylindrical vessel with 20 orifices on its side [91,92]. The polymer solution flew into the vessel through a rotary joint on the top of the vessel. The bottom end of the vessel was mounted on a rotary DC motor. Under a constant rotating speed, the diameter of the as-spun nanofibers was controlled by adjusting the polymer flow rates [91,92]. The conductive collector is another important part of the electrospinning set up. A flat collector, as the most common type of electrospinning collector, is used to prepare randomly oriented nonwoven electrospun mats. Well-aligned and highly ordered electrospun mats are always required in tissue engineering projects. In the past few years, a series of new collectors including rotating cylinders [93], wheel-like disks [94], and auxiliary electrode/electrical fields [95] have been designed, and well-aligned electrospun mats have been fabricated [96].

Although the set up for electrospinning is extremely simple as shown in Fig. 1A, the spinning mechanism is complicated and sensitive to a number of parameters. Electrospinning nanofibers with a uniform diameter remains challenging due to an insufficient understanding of the mechanism behind the instability and splaying process of the polymer jet [12]. The diameter and morphology of electrospun fibers can be adjusted by three types of parameters: solution parameters (e.g., surface tension, polymer molecular weight, polymer concentration, conductivity and dielectric constant), process parameters (e.g., applied voltage, spinneret-to-collector distance, the feeding rate for the polymer solution, and environmental parameters (e.g., relative humidity and temperature)). The size and shape of the fibers can also be modified by using different nozzle designs and conductive collectors. For example, increasing the electrical conductivity of the polymer solution is an efficient way to decrease the average diameter of the fibers, but too much increasing will prevent the formation of fibers. The solidification of electrospun fibers is almost completely influenced by the evaporation rate of the solvent. It should be completed before the sample reaches the collector; otherwise post-crosslinking processes are occasionally required for

further crosslinking. Although the electrospinning process is simple, solvent evaporation is one of the critical problems, since evaporation rate controlling remains challenging and the vapors of the organic solvents are usually toxic. Another disadvantage of electrospinning is that the fibers are directly collected onto a collector, making it nearly impossible to handle a single fiber.

Compared to electrospinning, microfluidic spinning is influenced by less parameters. The wet environment in the microfluidic spinning process contributes to the encapsulation of sensitive materials such as cells. Cells could be simply and safely encapsulated in fibers by introducing a cell suspension in a solution before solidification occurs in the microfluidic channels. Microfluidic spinning uses an eco-friendly aqueous system, which is of less environmental concern than electrospinning [97,98]. In contrast, real time and spatiotemporal control of the shape, size and composition of the fiber is possible when employing microfluidic spinning. Such control is one of the fascinating features of the microfluidic method. Another critical feature of microfluidic spinning is its ability to handle individual fibers and to assemble a 3D fibrous structure by reeling, weaving, and direct writing. Lee et al. assembled a bio-artificial liver chip by continuous winding of HepG2-cultured chitosan microfibers with a rotating fiber winder [69]. Onoe et al. proposed a microfluidic handling of cell-laden microfibers using a thin tube and fluid flow [79]. Using this handling approach, centimeter-scale woven structures could be fabricated by the use of a laboratory-made loom in culture medium. Recently, a microfluidic direct writer that integrated the concept of direct writing and microfluidic fiber spinning was developed to create a 3D cell-laden hydrogel construct that was deposited layer-by-layer on a substrate using computer-controlled operating systems [65,99].

2.4. Fiber morphologies

As mentioned above, the electrospinning method is sensitive to several parameters, such as the strength of the applied electric field, polymer concentration, solvent selection, shape of the needle, and tip-to-collector distance. Manipulation of these parameters can fabricate fibers with desired morphologies such as those with

porous, solid, core-shell, hollow or hybrid structures (Fig. 3). By adjusting these parameters, the diameter of as-spun fibers can be tuned from nanometers to a few micrometers. Although all of the parameters mentioned above affect the diameter of the fiber, the major ones are polymer concentration, the electrical conductivity of the polymer solution, the electrical field strength, and the feeding rate for the polymer solution [20,100]. Generally, an increase in polymer concentration or feeding rate leads to the formation of fibers with large diameters. On the other hand, an increase in the conductivity of the polymer solution always leads to fibers with small diameters. The effect of external electrical field strength on the diameter of the fiber is a little complicated. While a higher electrical field strength in general leads to a bigger fiber diameter, an initial decrease in fiber diameter with a specified increase in electrical field strength has also been reported [20]. The effect of other parameters such as surface tension and needle diameter on fiber diameter has been observed to be relatively small [20].

Solid interiors, circular cross-sections, and smooth surfaces are the typically observed features of electrospun nanofibers, while core-shell/hollow and Janus/hybrid nano/microfibers are also achievable by using co-axial-channels and side-by-side needles, respectively. Recently, four-layered nanofibers were successfully prepared using a four-needle coaxial device [101]. In addition, porous nanofibers have been prepared by either selectively removing one component inside composite fibers or judiciously inducing phase separation of the polymer inside single-component nanofibers (Fig. 3) [102]. Although the presence of beads in electrospun nanofibers is usually thought of as a problem, sometimes these beads also can be thought of as a type of pattern along the thin nanofibers (Fig. 3). Nanofibers are often deposited on the surface of a static collector as randomly oriented, nonwoven mats. Electrospun nanofibers can be simply aligned in order to improve the mechanical properties of both the individual fiber and the mat. Aligning fibers is achieved simply by using either a rapidly rotating collector or a conductive collector with an appropriate spatial arrangement of electrodes [103]. Such a well-aligned and highly ordered architecture is very useful for cells aligning [104].

The diameters of fibers fabricated using microfluidic spinning

Table 1
Comparison of electrospinning and microfluidic spinning.

Features	Electrospinning	Microfluidic spinning
Principle	<ul style="list-style-type: none"> - Viscoelastic polymer jet - Electrostatic force as driving force - polymer aggregation - Solvent evaporation/ 	<ul style="list-style-type: none"> - Coaxial laminar flow - Crosslinking (physical, chemical, ion, polymerization) - Hydrogel - Hydrophilic polymers
Materials	<ul style="list-style-type: none"> - Wide range of polymers for selection - Highly volatile solvents 	<ul style="list-style-type: none"> - A few hydrophobic polymers (e.g., PLGA) - Water is the most commonly used solvent
Fabrication process	<ul style="list-style-type: none"> - Relatively simple but overly sensitive fabrication process - Scale-up of fabrication is possible (e.g., needleless electrospinning) - Toxic gas generation 	<ul style="list-style-type: none"> - Not sensitive to several parameters - Relatively slow; time consuming - No toxic gas is generated since water is the main solvent and crosslinking is the typical fixing method
Environment	<ul style="list-style-type: none"> - Dry - Constant temperature and humidity 	<ul style="list-style-type: none"> - Wet - Room environment
Fiber diameters	<ul style="list-style-type: none"> - Nanometers to few microns 	<ul style="list-style-type: none"> - Nanometers to a hundred microns
Morphologies	<ul style="list-style-type: none"> - Alignment is possible at fabrication - Fibers with diverse morphologies have been fabricated (beaded, core-shell, porous, flat, etc.) 	<ul style="list-style-type: none"> - More diverse and tunable morphological features (patterning, coding) - Allows for handling of single fibers - High
Reproducibility of the fiber diameter	<ul style="list-style-type: none"> - Low 	
Physical/mechanical properties	<ul style="list-style-type: none"> - 2D with a large surface area - High density, small pores - Diversified mechanical properties due to a wide range of materials that can be selected 	<ul style="list-style-type: none"> - Low mechanical strength because of the hydrogel nature - High porosity
Applications in tissue engineering/drug delivery	<ul style="list-style-type: none"> - Scaffold is most popular - Encapsulation is difficult - Controllable drugs carrier 	<ul style="list-style-type: none"> - Cell encapsulation is the inherent advantage - Better regulation of cells - Limitations in drug loading (fast release, small scale, drug loss)

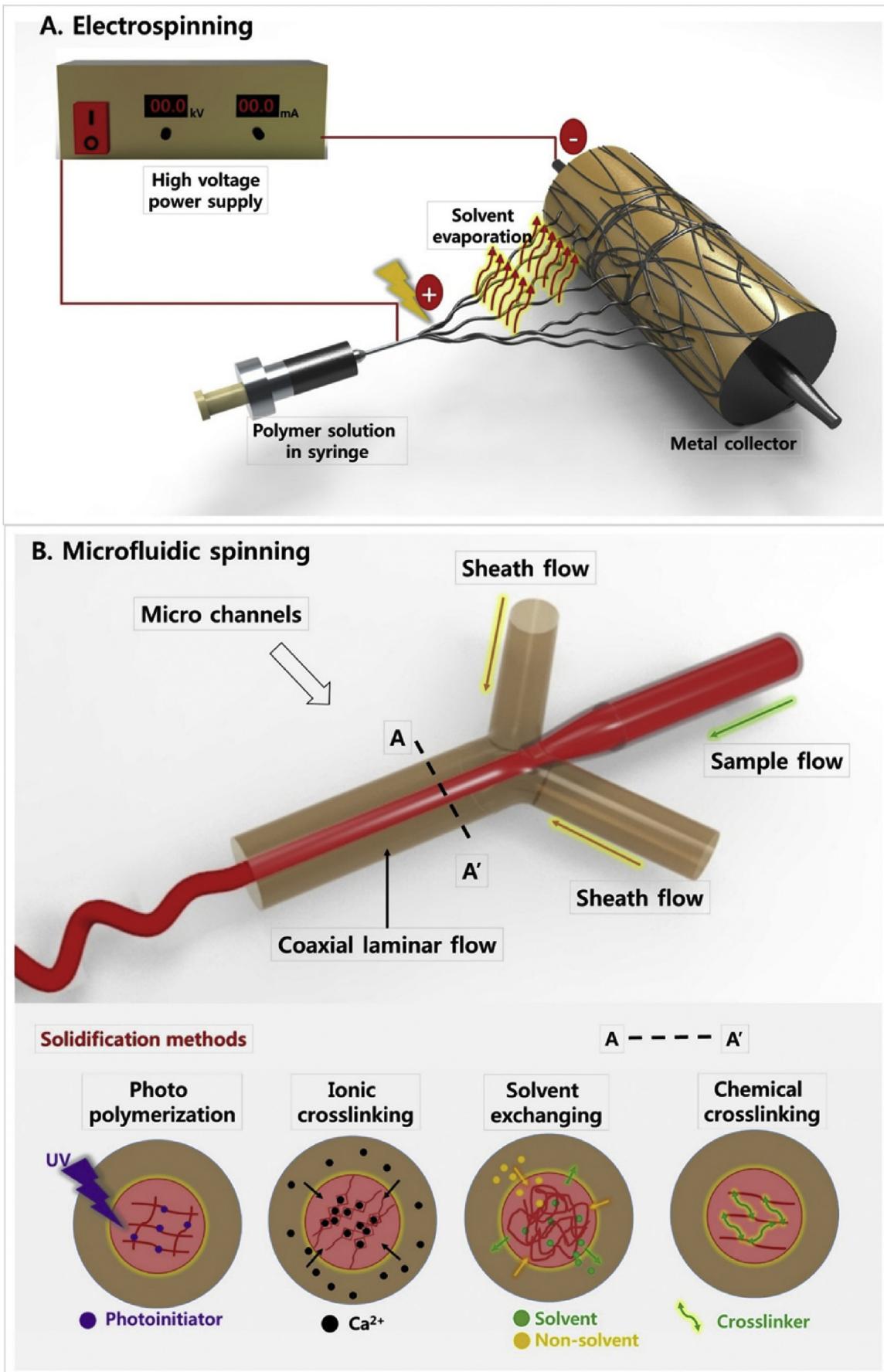


Fig. 1. Overview of electrospinning (A) and microfluidic spinning (B).

varies from a few micrometers to several hundred micrometers. It can be precisely controlled by changing the channel dimensions and the flow rates of the core and sheath solutions (Fig. 4). In general, fibers fabricated using microfluidic systems are larger than electrospun fibers [98]. In principle, scaling down of structures to nanometer range using microfluidic spinning platforms is challenging due to the difficulties associated with fabricating nanoscale microfluidic chips and injecting fluids into the narrow channels [21]. Recently, a nano-scale alginate fiber (<100 nm) with a crystal-like structure was spun using IPA as the sheath flow [48]. IPA induced the dehydration of alginate, resulting in the formation of numerous nanostrands. The shear force in the microfluidic channel further aligned these nanostrands to form a compact structure, leading to the formation of very thin fibers [48]. Depending on the design of the microfluidic devices and the materials, fibers with a variety of shapes and geometries could be produced (Fig. 4), such as core-shell fibers [79,105], tubular (hollow) fibers [9,33,37,43,46,68,70,72,73,106–110], parallel fibers [58,62], Janus (asymmetric, hybrid) fibers [9,45,49,55,56,111,112], porous fibers [66–68,111,113], grooved fibers [45,47], and flat fibers [32,34,39,47,58,62,114–117] (Fig. 4). The variety of shapes provides diverse microenvironments for aligning cells in cell culture and engineering of tissues such as nerve tissue. Moreover, patterning multiple materials along the fiber direction has also been developed using digital valve control systems. Kang et al. proposed a novel microfluidic spinning method for producing tunable physiochemical coding systems, and diverse materials were coded along the fiber [45]. Such a capability of producing patterns can be used for the spatiotemporally programmed loading of cells or drugs with a programmable release profile. The details of such carriers will be described later. Leng et al. developed a one-step synthesis of mosaic patterned flat fibers for cell patterning [62]. Besides physiochemical coding along the fiber as mentioned above, microfluidic-spun alginate fibers can be used as a temporal structure to support the growth of cellular constructs. Alginate hydrogels can be enzymatically digested by using alginate lyase without harming cells [118]. This characteristic makes it possible to remove the alginate hydrogel from assembled macroscopic cellular constructs when it is desirable or necessary to have the alginate hydrogel function as a temporal or sacrificial structure [52–54,60,61,77,107,119]. Using this method, Hammer et al. introduced microchannel-like pores into 3D hydrogels by removing encapsulated microfluidic-spun alginate fibers [53].

3. Applications

In consideration of the significance of the applications of the fibers produced by electrospinning and microfluidic spinning, we summarize some typical biomedical applications of these fibers in this section (Table S2 and S3) according to target organs, loaded cells or molecules, unique features for biomedical applications, fiber morphologies, fabrication process and materials. The details of these applications are described in this section.

3.1. Fibers as scaffolds

3.1.1. Electrospun nanofibers as scaffolds

The nonwoven electrospun nanofiber network resembles the ECM fairly well. This resemblance is a major advantage of electrospinning because it opens up the possibility of mimicking the ECM environment highly. The ability to carry out a simple fabrication of scaffolds using electrospinning was first shown by Li et al., in 2002 [120]. The nanofibrous scaffold they fabricated successfully mimicked the natural ECM scaffold architecture, specifically with regards to the fiber diameters, high porosity, and mechanical

properties. The fabricated scaffold exhibited favorable cell adhesion and proliferation, and the fiber orientation helped guide the growth of the seeded cells. This study opened up a myriad of possibilities in artificially fabricated scaffolds, and thus ever since, there have been active researches regarding scaffold fabrication using electrospinning in many niches of tissue engineering. Electrospun nanofibers have already been tested for various tissue engineering applications as shown in Table S2, Fig. 5 and Fig. 7A.

Wound dressings and skin tissue: Skin consists of two main layers, an outer epidermis layer and an inner dermis layer, which are made of keratinocytes and fibroblasts, respectively [121]. Skin protects the inner organs from the external environment, however the regeneration rate is relatively slow in the case of burned skin. In skin wound repair, bacterial invasion and dehydration are the most common issues. Therefore rapid restoration of the epithelial barrier function is a crucial mission to wound dressing and skin tissue regeneration [122]. The small pore size of the electrospun mat is able to protect the wound from infection and dehydration during healing, therefore electrospun nanofibrous mats constitute a good candidate for wound dressings and skin tissue engineering. Various natural and synthetic polymers, such as chitosan, PCL, PEO, PU and PVP, have been electrospun into mats for wound dressings [123–128]. Functional materials such as silver nanoparticles and growth factors have been co-electrospun with polymers to improve the antibacterial properties and healing efficiency of the mat. Electrospun mats hold great promise in skin tissue engineering due to their ECM-like structure. The migration of keratinocytes has been shown to be significantly stimulated on the collagen-gel-coating PCL mats [122]. Epidermal induction factors that were encapsulated in core-shell PLLCL/gelatin nanofibers showed sustained release. A higher percentage of adipose-derived stem cells (ADSCs) differentiated into epidermal lineages on the electrospun mat, showing the potential of such mats for use in skin tissue engineering application [129].

Bone regeneration: Bone tissue is typically made up of bone matrix, which is a composite material composed of type I collagen fibers and hydroxyapatite nanoparticles. Collagen nanofibers provide bone a structural framework, while hydroxyapatite nanoparticles provide rigidity and compressive strength [130]. Electrospun nanofibrous mats containing hydroxyapatite nanoparticles have been fabricated to mimic natural bone matrix. Various polymers, such as PCL-PEG-PCL, chitosan, PEO, silk fibroin and gelatin, have been co-electrospun with hydroxyapatite nanoparticles to prepare natural bone-matrix-like scaffolds for use in bone regeneration [131–135]. These composite nanofibrous scaffolds have been observed to promote cell proliferation and mineral deposition and showed a great potential for application in bone regeneration. PCL-PEG-PCL nanofibers containing 30 wt% of hydroxyapatite nanoparticles were implanted into the muscle pouches and showed good biocompatibility to surrounding tissue. And this composite scaffold repaired the rectangular full-thickness calvarial defects in New Zealand white rabbits [131]. Bone-mimetic electrospun scaffolds consisting of PCL, collagen I, hydroxyapatite nanoparticles and PEO were fabricated and enhanced the proliferation of mesenchymal stem cells, suggesting these matrices serve as promising degradable substrates for osteoregeneration [132]. Incorporation of PEO sacrificial fibers into scaffolds increased scaffold pore size and promoted mesenchymal stem cells infiltration into scaffolds *in vitro*. The infiltration of endogenous cells was also promoted when scaffolds were placed within calvarial organ cultures [132]. Chitosan/hydroxyapatite were electrospun and further crosslinked with genipin as potential substitutes for periosteum [133]. This scaffold supported adhesion, proliferation and osteogenic differentiation of mouse 7F2 osteoblast-like cells [133]. Biomimetic gelatin/hydroxyapatite nanoparticles composite

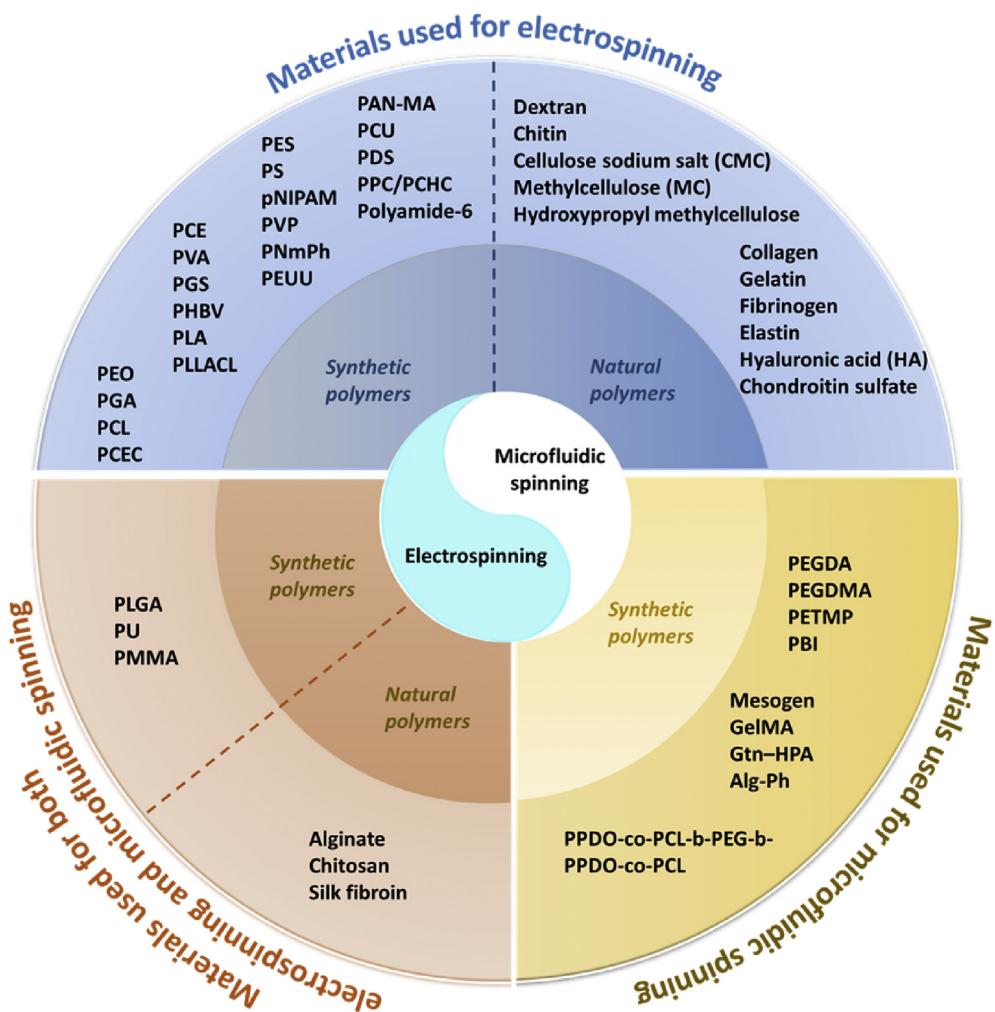


Fig. 2. Materials used for electrospinning and microfluidic spinning.

nanofibers were fabricated by electrospinning lyophilized gelatin/hydroxyapatite nanoparticles/organic solvent matrix [135]. This nanocomposite scaffold improved the bone-derived cellular activity significantly when compared to the pure gelatin scaffold [135].

The incorporation of hydroxyapatite nanoparticles in electrospun scaffolds was shown to improve the mechanical properties of the scaffold. Other nanoparticles such as silica nanoparticle have also been incorporated in PCL nanofibers to improve the mechanical properties and bioactivity of the scaffold [136]. Conductive carbon nanotubes (CNTs)/PLA composite nanofibers fabricated by electrospinning possessed great potential application in bone regeneration [137]. Both the electrical stimulation and topographical features of the composite nanofibers improved the functions of osteoblasts [137]. Besides scaffolds based on nanoparticle/polymer nanofibers as mentioned above, a bone-matrix-mimicking scaffold based on a different design concept has also been reported [138]. A core/shell polyamide-6/calcium lactate composite fibers were fabricated by combining an electrospinning with surface neutralization process [138]. First, polyamide-6/lactic acid core-shell fiber was fabricated by simple electrospinning, and then the lactic acid shell was converted into calcium lactate via neutralization using calcium base. The composite polyamide-6/calcium lactate fibers significantly enhanced the deposition of calcium phosphate when incubated in biomimetic simulated body fluid and showed potential for applications in bone tissue engineering [138].

PLGA/PPHOS electrospun nanofibrous mats that were rolled up into a 3D fiber-layered concentric structure with an open central cavity showed similar structural and mechanical features as native bone matrix. This 3D structural design was shown to significantly enhance the proliferation, infiltration and ECM secretion of osteoblasts [139]. Growth factors and drugs encapsulated in nanofibers play a critical role in bone tissue engineering. Incorporating growth factors such as bone morphogenetic protein 2 (BMP-2) into hydroxyapatite nanoparticle/nanofiber scaffolds was another good method for regenerating bone [140]. Silk/PEO/BMP-2/hydroxyapatite nanoparticle nanofibers were used for *in vitro* bone formation from human bone marrow-derived mesenchymal stem cells [140]. The incorporation of BMP-2 and hydroxyapatite nanoparticles into the scaffolds enhanced calcium deposition and transcript levels of bone-specific markers [140].

Connective tissues (ligaments, tendons, insertion sites, the knee meniscus and periodontal tissue): Without considering the special connective tissue such as bone, blood vessel and cartilage, connective tissues can be broadly subdivided into dense connective tissues and loose connective tissues [141]. Normal healthy dense connective tissues are mainly composed of closely packed type-I collagen fibers and fibroblasts, forming strong structures such as ligaments and tendons [141]. Tendons connect muscles to bone, while ligaments connect bones to bones. The loose connective tissues hold organs in place and tightly bind epithelial tissue to

other underlying tissues. In loose connective tissues, the principal cellular element is also fibroblasts [141]. Because cells can be well oriented on aligned electrospun mats, aligned nanofibers have been widely used to orient cell growth for regeneration of tissues such as nerves, vascular tissue, muscle and dense connective tissue, in which cells are highly ordered to ensure the functionality of the tissue. Besides, scaffolds made of aligned fibers always show better mechanical properties than those made of randomly oriented fibers. Randomly oriented electrospun nanofibrous scaffolds were tested and did show potential for regeneration of ligaments and tendons [142–145]. Nevertheless, aligned electrospun nanofibrous scaffolds are suitable candidates in the tissue engineering of tendons and ligaments, as well as of the knee meniscus, since the aligned electrospun scaffolds provide mechanobiological cues similar to those of the native ECM of tendons and ligaments. Aligned electrospun PLA nanofibers are the most widely used materials for tendon/ligament regeneration due to their good biocompatibility, biodegradability and mechanical properties [146]. Parallel electrospun nanofibers based on other polymers such as PU and chitosan were also tested and showed a potential for tissue engineering of dense tissues [147,148]. Lee et al. developed a highly aligned PU nanofiber matrix, and assessed the ECM generation of human ligament fibroblasts on this nanofiber matrix in response to the fiber alignment and direction of mechanical stimuli [147]. On the matrix, human ligament fibroblast had a similar morphology to ligament fibroblasts *in vivo*, and the production of ECM was also enhanced when cultured on aligned PU nanofiber matrix [147]. Zhang et al. fabricated well-aligned chitosan-based electrospun fibers which enable tenogenic differentiation of human-induced pluripotent stem cells (hiPSCs) *in vitro* and *in vivo* [148]. In situ rat Achilles tendon repair study further confirmed that aligned chitosan fiber scaffold regulated hiPSC-MSCs differentiation and thus promoted tendon repair [148]. The aligned nanofibers have also been twisted or braided into more complicated 3D structures, which are much more similar to the structure of the native ECM of the dense connective tissues. Li et al. fabricated braided nanofibrous scaffolds by braiding three, four, or five aligned bundles of PLA electrospun nanofibers to mimic the native collagen bundles [149]. The performance of the braided nanofibrous scaffold was very similar to the performances of native tendons and ligaments during load.

Electrospun nanofibers have also been used for the regeneration of insertion sites, which are the interfaces between ligaments and bones or between tendons and bones. The ECM of insertion sites exhibits structural, mechanical and chemical gradients [150–152]. Collagen fibers are highly aligned in tendons and ligaments, and become less aligned closer to the insertion site [150]. A series of novel electrospun scaffolds with structural or chemical gradients have been prepared and showed great potential for insertion site regeneration [151–153]. Xie et al. fabricated “aligned-to-random” electrospun PLGA nanofiber scaffolds that mimic the structural organization of collagen fibers at the tendon-to-bone insertion site [151]. Rat tendon fibroblasts were aligned on the aligned portion of the scaffold while cells were randomly oriented on the random portion [151]. Li et al. developed a simple immersion method for generating a gradient coating of calcium phosphate on a nonwoven mat of electrospun nanofibers [153]. A gradient in calcium phosphate along the fibrous mat was controlled by varying the immersion time in simulated body fluid. The gradient in mineral composition on the scaffold significantly influenced the activity of the seeded mouse preosteoblast MC3T3 cells [153]. With a goal of regenerating ligament-bone interface, Samavedi et al. fabricated a continuously graded mesh by co-electrospinning hydroxyapatite nanoparticles/PCL and PEUU solutions from offset spinnerets. After selective deposition of mineral crystallites on the

hydroxyapatite nanoparticles/PCL fibers by treatment with simulated body fluid, a gradient of tensile modulus along the length of the mesh was formed [152]. And MC3T3-E1 osteoprogenitor cells were metabolically active when cultured on the graded mesh [152]. In addition, electrospun nanofibrous scaffolds have also been tested and showed considerable potential for regeneration of other connective tissues such as the knee meniscus and periodontal tissue [154,155]. Qu et al. developed composite electrospun PEO nanofibrous networks in which collagenase was encapsulated, and released upon hydration [154]. After implantation, the encapsulated collagenase was released and these novel scaffolds significantly enhanced the repair of knee meniscus in both a subcutaneous xenotransplant (rat) model and an orthotopic meniscal injury (ovine) model [154]. Zamani et al. fabricated metronidazole benzoate-loaded PCL nanofibers by electrospinning [155]. A sustained release of the encapsulated metronidazole benzoate was achieved for at least 19 days. This system could be used for locally controlled delivery of metronidazole benzoate in periodontal diseases [155].

Cartilage: The native ECM of articular cartilage is a unique environment composed of protein fibers and a ground hydrogel substance, which contributes to the unique mechanical properties of articular cartilage [156]. Articular cartilage has a limited ability to self-repair after injury because of the tissue avascularity and the low mitotic activity of chondrocytes [156]. Both aligned and randomly oriented electrospun nanofibrous scaffolds have been used in cartilage tissue engineering. Electrospun PVA nanofibrous scaffolds coated with chondroitin sulfate as biological cues were prepared for the regeneration of articular cartilage [156]. When implanted into rat osteochondral defects, PVA fibrous architecture of the scaffolds enhanced the production of sulfated glycosaminoglycan, and the presence of chondroitin in the fibers accelerated the synthesis of type II collagen [156]. Gelatin/PCL composite nanofiber mats were prepared and tailored into different 3D structures for cartilage regeneration. Chondrocytes were seeded between these electrospun mats to form a sandwich-like structure. Cartilage tissues with good elasticity and impressive mechanical stretch were successfully formed both *in vitro* and *in vivo* [157,158]. In addition, randomly oriented electrospun PLA and PCL/PVA composite nanofibrous cell-laden scaffolds were fabricated and showed potential for cartilage regeneration [159,160]. Chen et al. fabricated PLA nanofibers by electrospinning, and further modified these randomly oriented PLA fibers with cationized gelatin to improve their compatibility with chondrocytes [159]. The scaffold supported chondrocyte proliferation, differentiation and cartilaginous matrix biosynthesis both *in vitro* and *in vivo* [159]. PCL/PVA electrospun nanofiber scaffolds seeded with rabbit bone marrow mesenchymal stem cells were fabricated and implanted into rabbit full-thickness cartilage defects [160]. Improved regeneration of cartilage was observed in animals treated with cell-seeded PVA/PCL scaffolds in comparison with untreated control and cell-free scaffolds [160]. Aligned electrospun PCL nanofibrous scaffolds with an organization similar to that of native collagen fibers in cartilage ECM have been prepared and tested for cartilage regeneration [161]. Human mesenchymal stem cells seeded on the aligned PCL scaffolds maintained the cell orientation even after 5 weeks, and the chondrogenic differentiation was significantly enhanced on the scaffolds [161].

Muscle: Muscles are highly oriented tissues with anisotropic properties. Natural repair of muscle damage is a complex process involving a coordinated action of a number of cell types. Although the natural repair system has a robust capacity to repair small, common muscle damages such as strains, tears, or lacerations, severe traumatic damages cannot be repaired by natural repair system [162,163]. Therefore, artificial scaffolds have been used to help

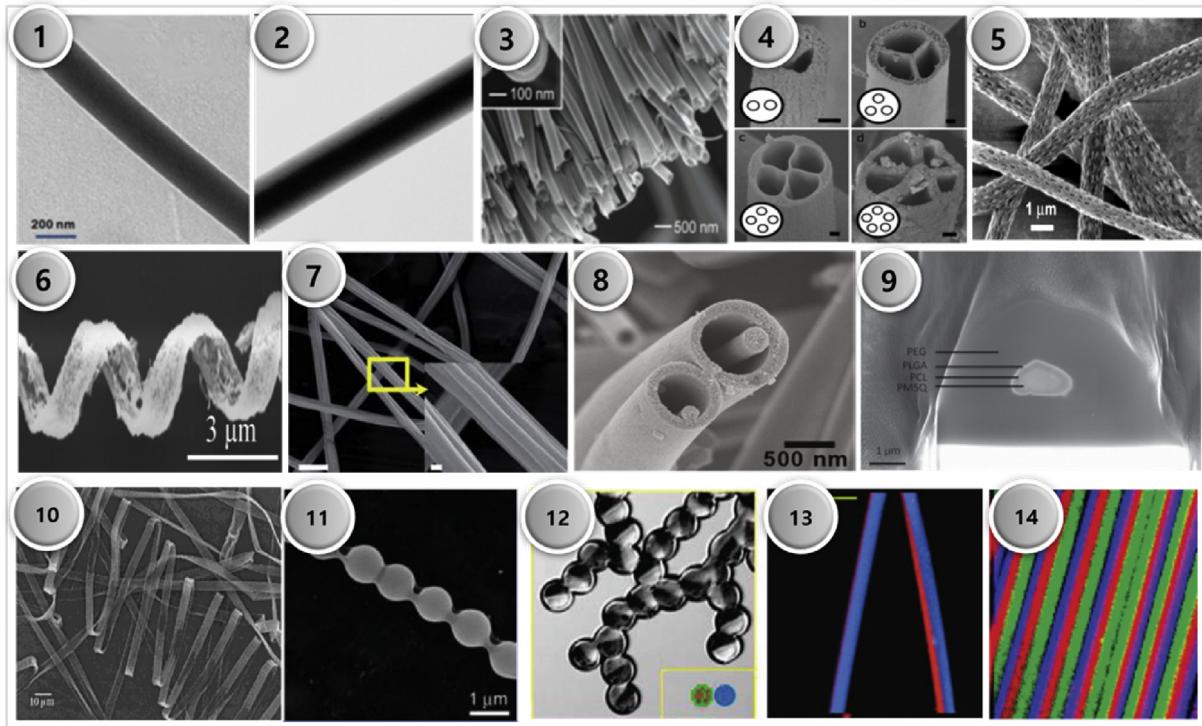


Fig. 3. Electrospun fibers with diverse shapes and dimensions. 1, Solid nanofiber (Reprinted with permission from [138]. Copyright 2013 Elsevier.); 2, Core/shell nanofiber (Reprinted with permission from [183]. Copyright 2014 Elsevier.); 3, Nanotube (Reprinted with permission from [207]. Copyright 2004 American Chemical Society.); 4, Multichannel microtubes (Reprinted with permission from [208]. Copyright 2007 American Chemical Society.); 5, Porous nanofiber (Reprinted with permission from [102]. Copyright 2001 John Wiley and Sons.); 6, Crimped fiber (Reprinted with permission from [209]. Copyright 2011 John Wiley and Sons.); 7, Grooved fiber (Reprinted with permission from [210]. Copyright 2011 Royal Society of Chemistry.); 8, Nanowire-in-Microtube (Reprinted with permission from [211]. Copyright 2010 American Chemical Society.); 9, Four-layered fiber (Reprinted with permission from [101]. Copyright 2014 John Wiley and Sons.); 10, Ribbon (Reprinted with permission from [212]. Copyright 2001 John Wiley and Sons.); 11, Beaded fiber (Reprinted with permission from [213]. Copyright 2010 American Chemical Society.); 12, Janus beaded fiber (Reprinted with permission from [214]. Copyright 2009 American Chemical Society.); 13, Janus fiber (Reprinted with permission from [215]. Copyright 2008 John Wiley and Sons.); 14, Multicompartmental fiber (Reprinted with permission from [214]. Copyright 2009 American Chemical Society.).

repair severe muscle damages. Both randomly oriented and aligned nanofibers electrospun from natural and synthetic polymers have shown potential for muscle tissue engineering [162–169]. Nevertheless, aligned electrospun nanofibrous scaffolds are much more attractive than those made of randomly oriented nanofibers and constitute one of the most prevalent types of materials used for muscle tissue engineering due to the intrinsic advantages of their native ECM-like structure and their substrate guidance cues. A highly aligned and electrically conductive electrospun PCL/PANI nanofibrous scaffold was fabricated and showed the potential for skeletal muscle tissue engineering [164]. Incorporation of PANI into PCL fibers significantly increased the electrical conductivity [164]. The aligned PCL/PANI nanofibers guided mouse C2C12 myoblasts orientation and significantly promoted myotube formation [164]. In addition, an aligned electrospun PCL nanofibrous scaffold with high porosity (99%) was prepared for heart valve tissue engineering [165]. Human adipose derived stem cells (hADSCs) and human valve interstitial cells (hVICs) penetrated into this porous PCL scaffold and populated the whole scaffold within 10 days [165]. In addition, the production of ECM by cells was significantly improved on this scaffold [165]. Furthermore, Kharaziha et al. developed a tough and flexible scaffold composed of aligned carbon nanotube/PGS/gelatin composite nanofibers for engineering cardiac constructs [168]. Here, incorporation of carbon nanotubes into electrospun nanofibers was shown to notably enhance the fiber alignment and toughness of the whole scaffold. Meanwhile, the beating properties of cardiomyocytes (CMs) were also significantly enhanced on this composite scaffold [168].

Nerve tissue: The nervous system is a complex arrangement of nerve cells including neurons and glial cells. Because adult central nerve system cannot be repaired on its own after physical trauma or disease, artificial scaffolds have been used to enhance the regenerative abilities of central nervous system neurons [170]. Effective scaffolds should help develop neural guidance conduits to bridge gaps in damaged peripheral or central neurons, and simultaneously direct axonal sprouting and promote neurotropic factors diffusion [171]. Aligned electrospun nanofibers have been widely used for nerve tissue engineering due to their ability to serve as a substrate that provides topographical guidance to neural cells and enhance the diffusion of neurotrophic factors. The importance of nanofiber alignment for directing the growth of neural stem cells, neurons, and glial cells has been demonstrated through testing many aligned electrospun scaffolds made of both natural and synthetic polymers [172–186]. Electrospun chitosan nanofibrous scaffolds showed particularly high potential for nerve tissue engineering [178]. Schwann cells grown on the aligned chitosan-PCL fibers highly oriented along the fiber alignment direction. PC-12 cells on the aligned fibers showed enhanced unidirectional neurite extension and up-regulation of differentiation-specific gene expressions [178]. Wang et al. fabricated a more complicated 3D structure based on electrospun chitosan nanofibers, called a chitosan mesh tube [176,177]. The tube was bridge-grafted over the nerve gap in a rat sciatic nerve defect. After 30 weeks, new nerves resembling the isograft were formed [176,177]. Aligned electrospun PLA nanofibers are also widely used for nerve tissue engineering [181,182]. Recently, electrically conductive materials such as gold

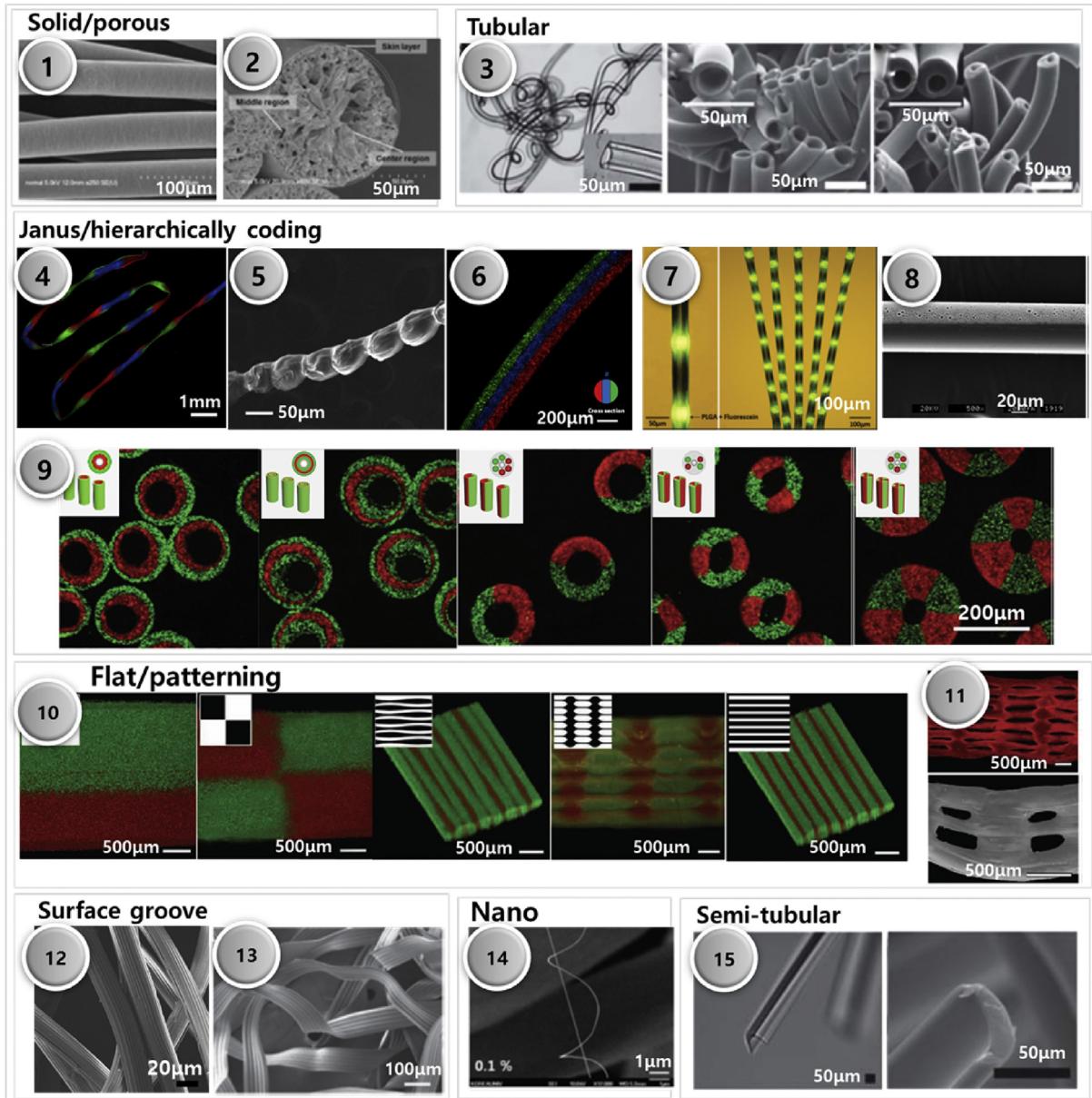


Fig. 4. Microfluidic spun fibers with diverse shapes and dimensions. 1, Solid fiber (Reprinted with permission from [66]. Copyright 2008 American Chemical Society.); 2, Porous fiber (Reprinted with permission from [66]. Copyright 2008 American Chemical Society.); 3, Tubular fiber (Reprinted with permission from [33]. Copyright 2011 Royal Society of Chemistry.); 4, Serial coding microfiber (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 5, Beaded microfiber (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 6, Parallel coding microfiber (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 7, Bamboo-like hybrid microfiber (Reprinted with permission from [216]. Copyright 2014 John Wiley and Sons.); 8, Janus microfiber (Reprinted with permission from [111]. Copyright 2009 Royal Society of Chemistry.); 9, Multicompartimental microfibers (Reprinted with permission from [201]. Copyright 2014 John Wiley and Sons.); 10, Mosaic hydrogel flat microfibers (Reprinted with permission from [62]. Copyright 2012 John Wiley and Sons.); 11, Void areas patterning flat microfiber (Reprinted with permission from [62]. Copyright 2012 John Wiley and Sons.); 12, Grooved microfiber (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 13, Grooved flat microfiber (Reprinted with permission from [47]. Copyright 2012 John Wiley and Sons.); 14, Nanofiber (Reprinted with permission from [48]. Copyright 2013 John Wiley and Sons.); 15, Semi-tubular microfiber (Reprinted with permission from [33]. Copyright 2011 Royal Society of Chemistry.).

nanoparticles were incorporated into aligned electrospun silk fibroin/PEO nanofibers and the resulting nanofibers showed considerable potential as a substrate for nerve tissue engineering [186]. The silk/PEO/gold nanocomposite based nerve conduit was found to promote adhesion and proliferation of Schwann cells *in vitro* and showed good biocompatibility with surrounding tissue *in vivo* [186]. Pre-seeding the conduits with Schwann cells was found to enhance myelination of the regenerated tissue. The animals implanted with the conduits exhibited near normal values of nerve conduction velocity, compound muscle action potential and

motor unit potential [186].

Blood vessels: Normal blood vessels, except capillaries, have three lamellar layers composed of different cells: the intima that contains a single layer of endothelial cells and prevents spontaneous blood coagulation, the media that consists of smooth muscle cells and provides optimal mechanical properties, and the adventitia that consists of fibroblasts and connective tissues [170]. Suitable matrices for blood vessel tissue engineering should be designed to mimic the distinct properties of the specific blood vessel regions. PCL, as an aliphatic polyester, is characterized by its

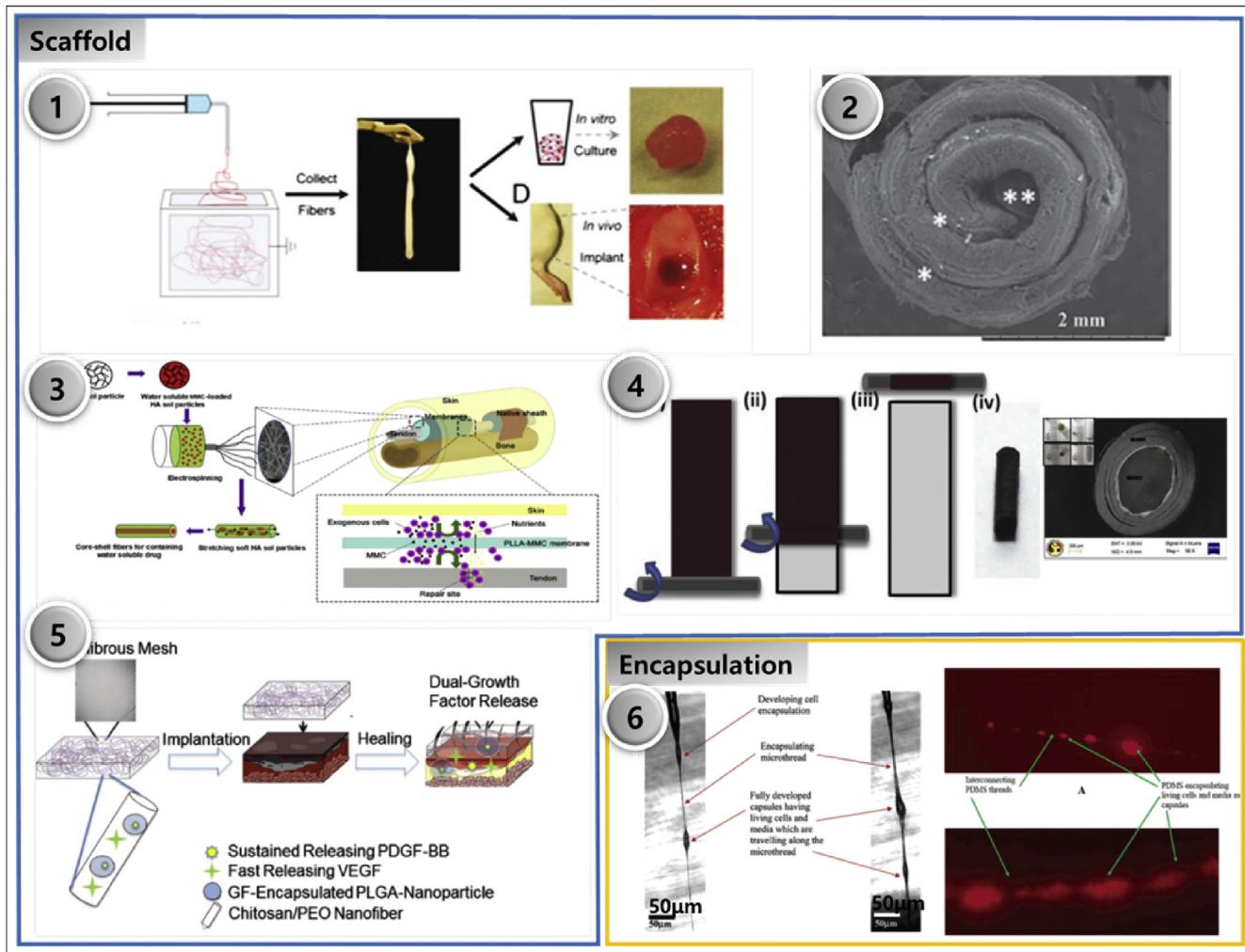


Fig. 5. Examples of electrospun fibers for use in tissue engineering. 1, PVA nanofibers for articular cartilage repair (Reprinted with permission from [156]. Copyright 2012 United States National Academy of Sciences.); 2, Biomimetic 3D PPPOS-PALGA electrospun scaffold for bone regeneration (Reprinted with permission from [139]. Copyright 2011 John Wiley and Sons.); 3, Mitomycin-C/hyaluronan-loaded PLLA electrospun membrane for tendon regeneration (Reprinted with permission from [143]. Copyright 2015 Elsevier.); 4, Nerve conduits fabricated by a novel electrospun sheet rolling method (Reprinted with permission from [186]. Copyright 2015 Elsevier.); 5, Electrospun mat embedded with two growth factors for wound healing (Reprinted with permission from [123]. Copyright 2013 Elsevier.); 6, Live cells encapsulated in electrospun fibers (Reprinted with permission from [194]. Copyright 2006 American Chemical Society.).

strong mechanical properties. Electrospun PCL nanofibers have been processed into various tubular scaffolds with sufficient mechanical strength and elasticity for blood vessel tissue engineering. Wang et al. fabricated a macroporous (~30 µm) electrospun tubular scaffold composed of thick PCL fibers (5–6 µm) [187]. *In vitro*, the scaffold stimulated the macrophage polarization into M2 phenotype [187]. *In vivo* implantation by replacing rat abdominal aorta was performed, and the scaffold enhanced cell infiltration, ECM secretion and vascularization [187]. Recently, Zhu et al. designed a bi-layered tubular scaffold composed of an inner layer of circumferentially aligned wet-spun PCL microfibers and an outer layer of randomized electrospun PCL nanofibers [188]. After the scaffold was implanted in the rat abdominal aorta, the circumferentially oriented vascular smooth muscle cells (VSMCs) and longitudinally aligned endothelial cells (ECs) were successfully regenerated without any thrombosis or intimal hyperplasia up to three months post implantation [188]. Masoumi et al. designed a tri-layered elastomeric scaffold composed of a middle layer of micro-fabricated PGS and two outer layers composed of electrospun PCL/PGS nanofibers; this scaffold showed tunable anisotropic mechanical properties similar to those of native heart valves [189].

Rayatpisheh et al. designed a circumferentially aligned tubular construct of human aortic smooth muscle cells by combining cell sheet technology and electrospinning [190]. Here, the cell culture substrate was based on a pNIPAM-grafting PDMS, and a small portion of this PDMS substrate was covered with aligned electrospun PCL nanofibers [190]. Because an intact cell sheet was obtained by simply decreasing the temperature, a tubular constructs with circumferentially aligned smooth muscle cells was easily generated. And smooth muscle cells in the tubular constructs retained contractile gene expression [190]. In addition, spider silk protein, gelatin and chitosan have been incorporated into electrospun PCL nanofibers to further improve cellular attachment and infiltration, and in turn the regeneration of blood vessels [191,192]. Xiang et al. fabricated a composite nanofiber tubular recombinant spider silk protein/PCL/gelatin scaffold. The scaffold well supported and maintained the phenotype of Sprague Dawley Rat Aortic Endothelial Cells for 7 days *in vitro* [192]. Zhao et al. fabricated a composite RGD-recombinant spider silk protein/PCL/chitosan small-diameter vascular scaffold [191]. The scaffold supported the cells attachment and promoted the proliferation and functioning of Sprague Dawley Rat Aortic Endothelial Cells. The scaffold supported

the growth of cells under physiologic conditions of blood flow *in vivo*, and remained stable and passable for at least 8 weeks in a SD rat abdominal aortic defect model [191].

3.1.2. Microfluidic spun fibers as scaffolds

Compared with electrospinning, microfluidic spinning is still in its infancy, at least in terms of its applications for tissue

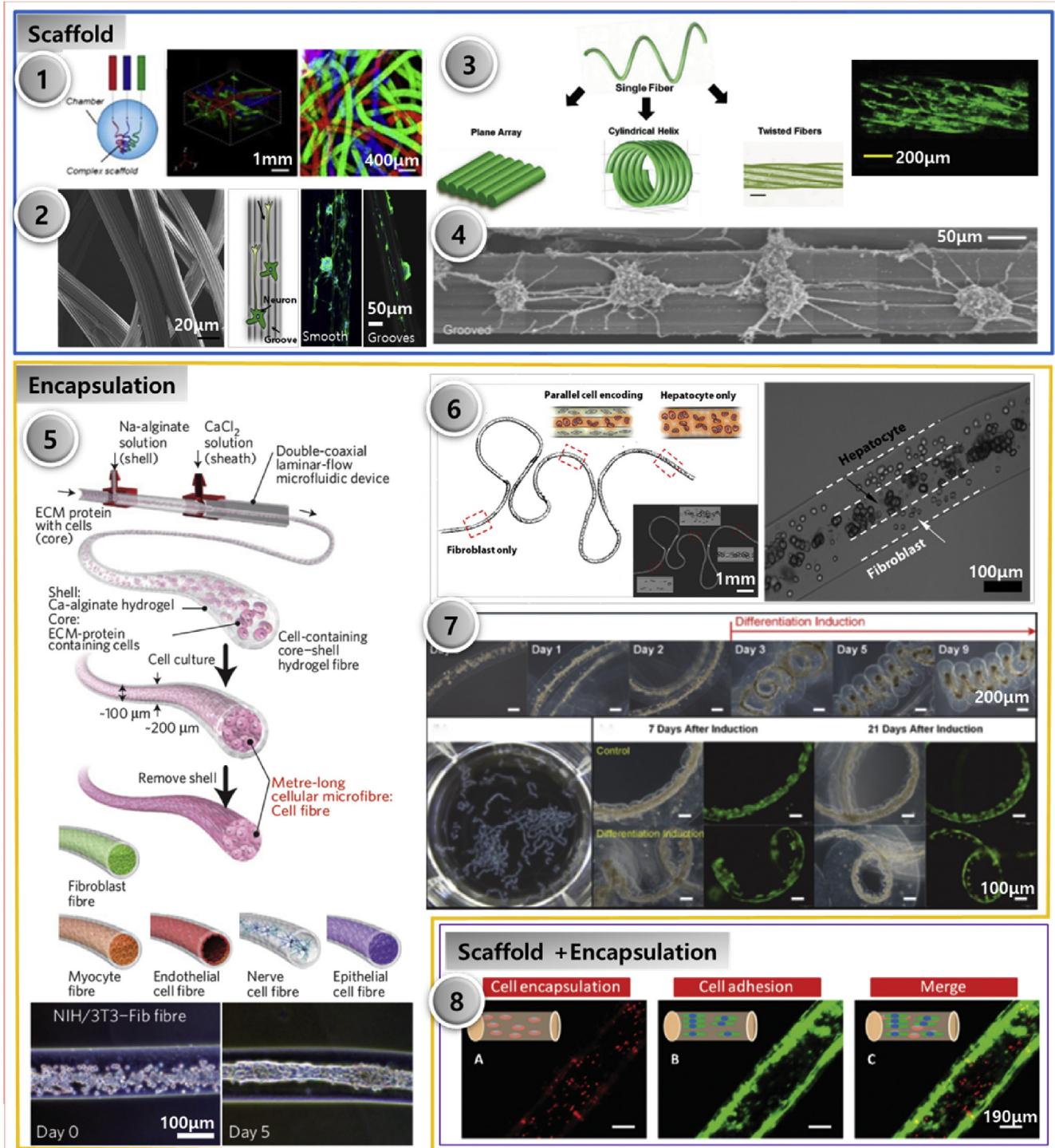


Fig. 6. Examples of microfluidic-spun fibers for use in tissue engineering. 1, Microfibrous 3D scaffold (Reprinted with permission from [49]. Copyright 2014 IOS publishing.); 2, Grooved cylinder microfibers for neuron alignment (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 3, 3D fibrous scaffold fabricated by assembling single microfibers (Reprinted with permission from [217]. Copyright 2014 John Wiley and Sons.); 4, Surface grooved flat microfibers for neuron alignment (Reprinted with permission from [47]. Copyright 2012 John Wiley and Sons.); 5, cellular fiber constructs fabricated by encapsulating diverse cells in hollow microfibers (Reprinted with permission from [79]. Copyright 2013 Nature Publishing Group.); 6, Spatial encapsulation of various types of cells in a single microfiber (Reprinted with permission from [45]. Copyright 2011 Nature Publishing Group.); 7, Coiled spring-shaped 3D cellular fibers containing circumferentially oriented smooth muscle-like cells (Reprinted with permission from [200]. Copyright 2015 Public Library of Science.); 8, A GelMA microfiber as a platform for both cell scaffolds and cell encapsulation (Reprinted with permission from [203]. Copyright 2015 John Wiley and Sons.).

engineering. The tissue engineering research based on microfluidic spinning is neither as comprehensive nor as systematic as that for electrospinning. Nevertheless, microfluidic spinning displays several advantages over electrospinning, such as the feasibility to handle single fiber and encapsulate cells and tissues, therefore it has the potential to regenerate more complicated tissues (Table S3, Fig. 6 and Fig. 7B). Compared to electrospun fibers, the practical applications of microfluidic-spun fibers are limited due to the lack of commercially available spinning devices. Recently, microfluidic chips for spinning are commercially available (MicroFIT <http://www.microfit.kr>; Micronit, <http://www.micronit.com>, etc.) and it is expected that they will be extensively applied. Microfluidic spinning offers scaffold products several advantages, such as intrinsically higher porosity, larger pore sizes and easy encapsulation of cells and cell spheroids [21–25]. Microfluidic spinning could provide spatiotemporal control of the composition, size and morphology of the material. Microfluidic-spun fibers can be wound on a spool or fabricated in a 3D mass. Park et al. developed a microfluidic spinning device for preparing 3D cell-laden fibrous scaffolds using a single microfluidic platform in a one-step process without the intervention of an operator [49]. The porosity values of fabricated fibrous scaffolds resulting from this device were measured to range from 0.23 to 0.52 and could be regulated by varying the flow rate. Moreover, rat hepatocytes encapsulated in this scaffold showed better viability and albumin secretion than did such cells encapsulated in a bulk hydrogel.

Since it is easier to design microfluidic device to fabricate complex fibers, therefore such fibers produced by microfluidic spinning are advantageous for (1) controlling cell alignment [45,47,67], (2) guiding cell proliferation [66,78], and (3) forming diverse shapes such as grooves, porous and flat structures by changing the geometry of the cross-section of the fluidic channel [77]. The surface of microfluidic-spun fibers with special surface patterns offers topographical cues for aligning myoblasts, cardiomyocytes and neuron cells [45]. The ability to align neurons and myoblasts is crucial for the engineering of nervous and muscular systems. Kang et al. prepared cylindrical fibers with engraved microscale grooves on the surface, and neuron cells seeded on the fiber surface were found to align themselves along the grooves [45]. They further improved this design, and flat fibers with superficial grooves have been fabricated [47]. The number of cells that could be seeded on the flat fibers was dramatically increased because of larger area. Neuron and myoblast cells on microgrooved flat fibers grew on the ridges and aligned along the grooves, while those cells on the smooth flat fibers formed randomly networked neurites or aggregates across the fiber surface. The flat fibers with aligned neuron cells could be directly implanted in spines or peripheral systems for nerve regeneration. This finding suggests that the microgrooved flat fibers could be an excellent candidate for regeneration of connective tissues and muscles where the assembly of highly aligned cells is crucial.

Scaffolds produced by microfluidic-spun fibers can be used for wound healing. Ahn et al. demonstrated the production of alginate fibers with a highly enhanced ampicillin loading capability [193]. The ampicillin-laden alginate fibers were prepared by using a calcium-containing IPA solution as the sheath flow. By the shear stress and repulsive reaction between alginate and IPA, the alginate chains were compactly aligned inside microfibers. Such compact alignment of alginate chains contributed to the delayed fiber degradation, and the sustained release of the encapsulated ampicillin. The ampicillin-loaded alginate fibrous scaffold was observed to promote the healing of a wound on the skin of a rat.

3.2. Fibers for cell encapsulation

3.2.1. Electrospun fibers for cell encapsulation

While there are numerous scaffold fabrication applications of electrospinning, cell encapsulation during electrospinning process is still challenging due to the harsh conditions of this method. However, recent technological developments have allowed for the fabrication of cell-laden fibers via electrospinning (Table S2 and Figs. 5 and 7A). In 2006, Townsend-Nicholson et al. first developed a coaxial needle set for “cell electrospinning”. In this method, a coaxial needle spinning system was used, and a concentrated cell suspension and medical grade PDMS were flowed through the core and the outer needle, respectively. The collected cell-bearing microfibers were successfully cultured with a cell viability comparable to that of the control cells [194]. Since then, other studies have explored the feasibility and practicality of cell electrospinning [195–197]. Electrospun cell-laden fibers have enabled the construction of 3D scaffolds for the engineering of tissues and organs, with the seeded cells completely infiltrated throughout the whole structure.

3.2.2. Microfluidic spun fibers for cell encapsulation

The applicability of cell encapsulation using microfluidic spinning technology has been recently extended to the *in vitro* reconstruction of complex 3D tissues mimicking organs such as liver and pancreas, and for immune protection [21]. With several advantages including mild spinning process and ability to produce fibers with diverse morphology, microfluidic spinning enables (1) immobilization of cells in solid or hollow-shaped fibers, (2) 3D co-culture systems with an ECM matrix using anisotropic or patterned fibers [45,49,56,58,62], (3) *in vivo* immunoprotection of implanted tissues for therapeutic purposes with the semi-permeable properties of hydrogels [50,79,198], and (4) microchannel formation by removal of alginate fibers from the 3D matrix [43,53,60,77,119,199].

Cell immobilization: Onoe et al. developed core/shell hydrogel microfibers using a microfluidic device with a double-coaxial laminar flow [79]. The core/shell fibers were composed of an alginate shell and a core made up of natural ECM proteins and cells. Cells encapsulated in the hollow core of the fibers proliferated and migrated along the longitudinal direction of the fibers; these cells connected with each other and formed fiber-shaped cellular constructs. Using this method, diverse cells were loaded into the fibers, such as myocytes, endothelial cells, nerve cells and epithelial cells. The fabricated cell-laden fibers showed functions of living tissues (Fig. 6, No.5) [79]. These functional fibers could be further weaved into more complicated macroscopic cellular structures to meet the more specialized needs of tissue engineering. Similarly, with the core/shell design, Lee et al. demonstrated the formation of a vascular structure by first encapsulating endothelial cells in alginate hydrogel shells of core/shell fibers and then embedding these fibers into smooth muscle cell-encapsulating bulk agar hydrogels [43]. Hsiao et al. fabricated smooth muscle-like tissue constructs by encapsulating de-differentiated fat cells (DFAT) in the core of alginate fibers [200]. Here, DFAT cells became elongated parallel to the axial direction of the fiber. After the DFAT cell fiber was formed in the core of alginate fibers, DFAT cells were subsequently induced to differentiate into smooth muscle cells. As the inherent traction forces of the cells increased, the DFAT cell fibers self-assembled into coiled spring constructs during differentiation into smooth muscle (Fig. 6, No.7).

Patterned co-culture: Natural tissues are always hierarchically composed of multiple types of cells. Microfluidic spinning can be used to encapsulate different cells into different compartments of a

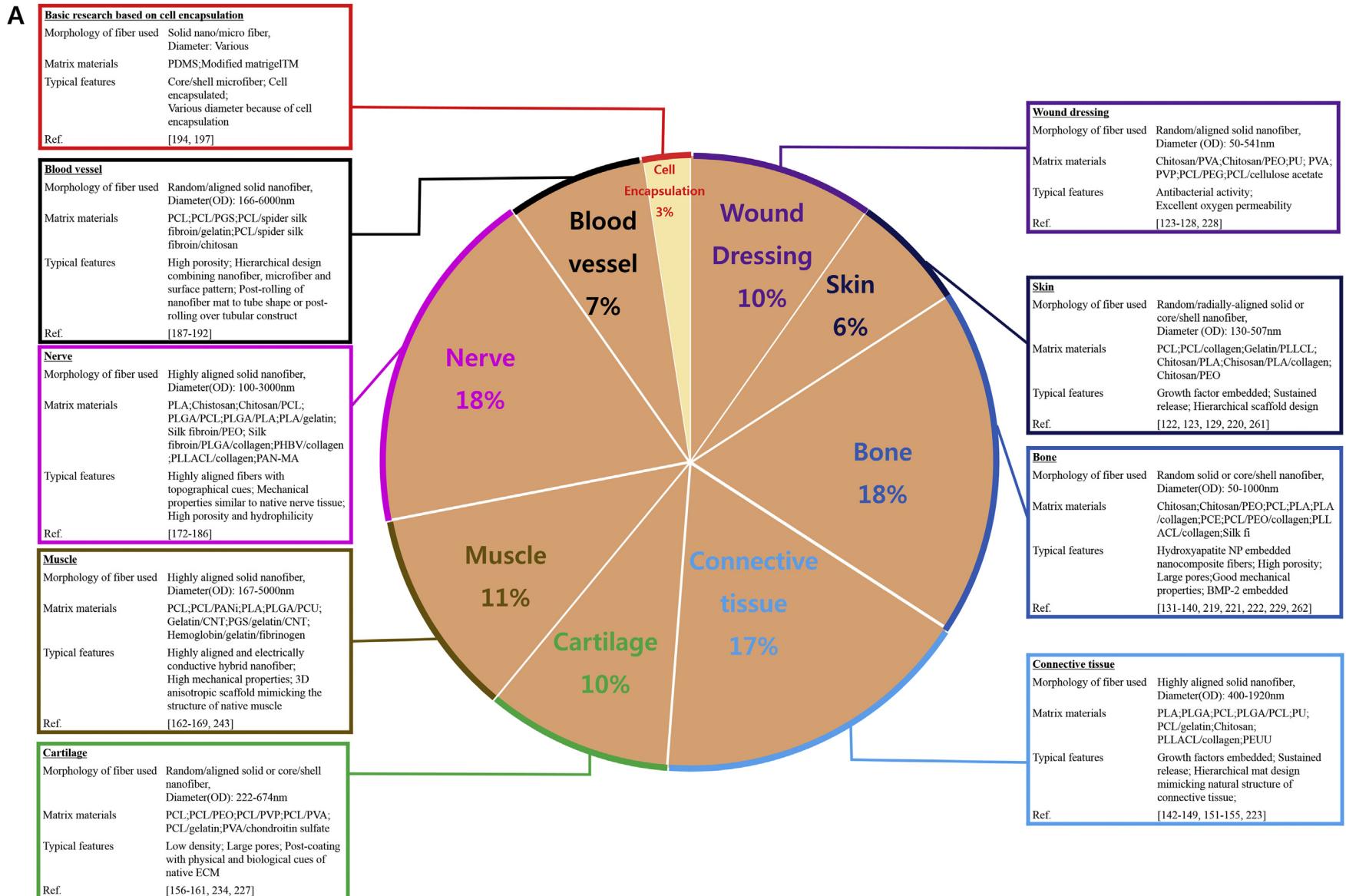


Fig. 7. Analysis of tissue-engineering-related papers that are summarized in Tables S2 and S3. (A) Electrospinning. (B) Microfluidic spinning [218–262].

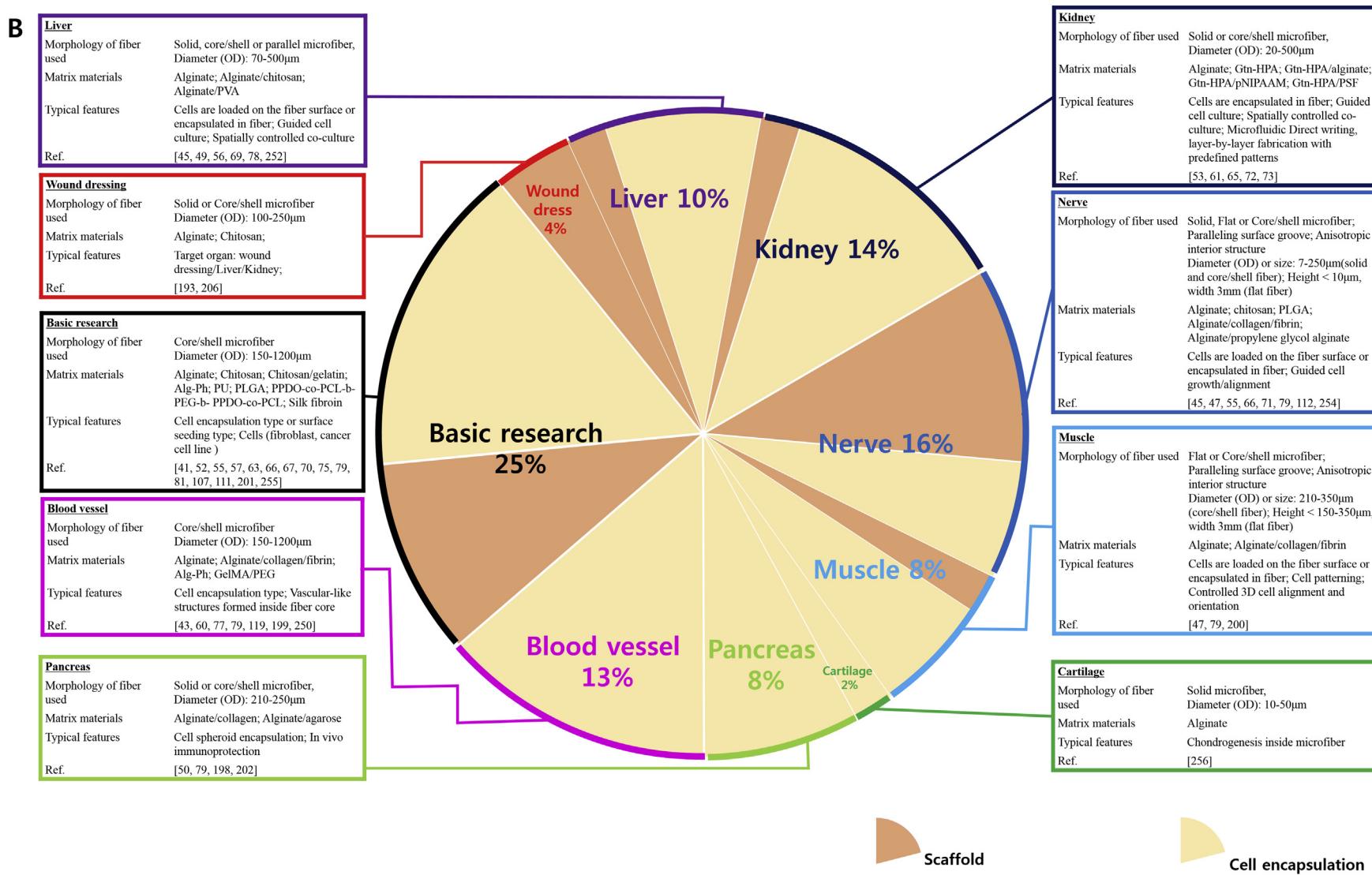


Fig. 7. (continued).

single fiber to regenerate more complicated tissues. Kang et al. encapsulated L929 fibroblasts and primary rat hepatocytes in the center and outer layers of a coaxial alginate microfiber, respectively, to prepare a liver-mimicking tissue structure (Fig. 6, No.6) [45]. Similar design concepts were implemented by Cheng et al. using a capillary coaxial microfluidic device. Multiple tapered barrel capillaries were coaxially inserted into a single collection capillary and different cells could then be encapsulated into different alginate compartments or layers [201]. Yamada et al. fabricated heterotypic hepatic micro-organoids by spatially encapsulating 3T3 cells in the fiber shell and hepatocytes in the fiber core, respectively. A scaffold-free hepatocyte-3T3 complex organoid was obtained after enzymatic removal of the alginate hydrogel [56]. They found that the obtained 3D organoids under high oxygen tension conditions had a very similar structure to the *in vivo* hepatic cord structures. Therefore, this microfluidic spinning based technique shows great potential for functional hepatic organoids fabrication and hepatocyte transplantation.

Immunoprotection *in vivo*: Most microfluidic-spun fibers display a hydrogel nature, and molecules can freely pass through the pores inside the hydrogel and hence be transported across the hydrogel wall. Therefore, when cells are encapsulated in microfluidic-spun fibers, the secreted molecules can easily diffuse out of the fibers into the surrounding tissue. Meanwhile, the hydrogel wall can efficiently protect encapsulated tissues from immune attack. As a result of these properties, these cell-encapsulating fibers can be used for the regeneration of complicated organ functions. The pancreas is one of the common examples. Jun et al. fabricated immunoprotective islets encapsulating collagen/alginate composite fibers and implanted these fibers into the intraperitoneal cavities of streptozotocin-induced diabetic BALB/C mice [202]. They found that the blood glucose levels of all the diabetic mice returned to normoglycemia within two to three days after implantation, and this normal level was maintained over one month [202]. They further improved this system using uniform hundred micron-scale cell spheroids instead of single cells [198]. Cell spheroids can better mimic the *in vivo* environment than single islet cells, and the spheroid structure hence improves cell viability. Onoe et al. encapsulated primary rat dissociated islet cells in alginate-agarose interpenetrating network hydrogel shells to form glucose-responsive insulin-secreting cell fibers. The cell fibers were injected and precisely folded into the subrenal capsular space of a diabetic mouse, and the blood glucose level remained normal over at least 13 days after implantation. When the cell fibers were removed from the renal parenchyma, all of the mice immediately became hyperglycemic again [79].

Microchannel formation: Construction of a well-distributed microvascular system is one of the critical challenging factors for the engineering of 3D tissues. This challenge may be overcome by using fibrous scaffolds. Lee et al. embedded endothelial-cell-laden microfluidic-spun hollow alginate fibers into a smooth muscle cell-laden agar-gelatin-fibronectin hydrogel, with both cells encapsulated inside the hollow fiber; the resulting hydrogel remained functional with an intact vascular structure for seven days [43]. Using the same design concept, Sakai et al. embedded human-endothelial-cell-laden phenol-substituted amylopectin microfluidic-spun fibers in a type I collagen hydrogel, followed by degrading the amylopectin fiber to form a tubular cavity and release of the encapsulated cells. The released cells grew on the surface of the tubular cavity and formed vascular structures [199]. Shi et al. developed cell-responsive grooved GelMA microfibers, and cells were encapsulated in the fiber and seeded on the grooved surface of the same fiber simultaneously (Fig. 6, No.8) [203]. The same fibers could be used to form cell scaffolds or encapsulate cells, which could facilitate the construction of more complicated tissues and organs.

3.3. Controlled drug delivery by fibers

Drug delivery is another intensely investigated subject of biomedical applications. The inherent high surface-to-volume ratio of electrospun nanofibers contributes to their high drug-loading capability and high encapsulation efficiency. Diverse drugs, such as antibiotics, anticancer drugs, DNA, RNA and proteins, have been successfully encapsulated in electrospun nanofibers, and their release kinetics have been studied [96]. Wound dressings and local chemotherapy are two of the most studied electrospun fiber-based drug delivery applications. Diverse antibiotics, such as tetracycline hydrochloride, ciprofloxacin, and levofloxacin, have been encapsulated in electrospun synthetic polymer fibers to heal wounds [96]. The release behavior of the loaded drug is controlled by both drug diffusion and fiber degradation rate. Recently, local chemotherapy based on electrospinning fibrous mats has attracted extensive attention because such mats can increase the local concentration of the drug and hence reduce its toxicity [96,204,205]. Yang et al. encapsulated doxorubicin-laden micelles in PVA/gelatin core-shell electrospun nanofibers [204]. After implantation, this delivery system achieved a high therapeutic efficacy using a very low dosage of drug, meanwhile the systemic drug exposure to normal tissues was efficiently reduced [204].

Until now, microfluidic spun fibers on the applications of drug delivery were less reported [193,206]. Generally, because of their hydrogel nature, microfluidic-spun hydrogel fibers are considered to be a highly promising candidate for loading and delivering bio-sensitive macromolecules or drugs. However, the large pores in the interior of the microfluidic-spun hydrogel fiber and the fast degradation of fiber materials hinder their applications for controlled delivery of small molecules such as ampicillin. Recently, we carried out a pioneering exploration and found that microfluidic-spun fibers could also serve as a good carrier for controlled drug delivery [193]. Instead of an aqueous sheath flow, a Ca-containing isopropyl alcohol solution was used as the sheath flow to crosslink the ampicillin-containing alginate fiber. As a result, alginate chains were well aligned along the longitudinal direction and densely compacted together due to solvent exchange-induced phase separation and shear forces inside the microchannel [48,193]. The highly ordered crystal-like alginate fiber structure contributed to the delayed degradation, and in turn to the high ampicillin-loading capability and the sustained release of entrapped ampicillin [193]. He et al. fabricated peapod-like chitosan microfibers with controllable and separate oil cores, and showed that they can serve as multi-compartmental micro-carriers for both water-soluble and oil-soluble molecules [206]. These microfibers are highly promising for the synergistic encapsulation of multiple drugs and developing drug-loaded medical patches for wound healing.

4. Conclusions and future perspectives

Micro-and nanofiber materials have demonstrated a variety of applications in biomedical field. These are mostly attributed to their tunable structures, flexible composites and biological functions, as well as the capability to mimic the *in vivo* like extracellular microenvironment. In this review, we compared the two different fibers fabrication methods in terms of their spinning principles, materials choice, and biological applications.

For electrospinning, many biocompatible and biodegradable synthetic and natural polymers could be directly electrospun into nanofibers for tissue engineering applications. Especially some synthetic polymers, such as PCL, PLA and PLGA, could offer the scaffold sufficient mechanical property for hard tissue engineering (e.g., bone), which could not be achieved by natural polymers. Highly aligned nanofibrous scaffolds, which favor the cell adhesion

and proliferation, could be fabricated through post-drawing or using special collectors. However, most of these synthetic polymers are hydrophobic. The hydrophobic surface of as-spun fibers lacks of cell-recognition signals, which greatly limit the application of electrospun fibers in tissue engineering. Therefore, the modification to the polymer material or scaffold surface would be expected to solve this limitation. Although the modification could widen the application of electrospun fibers, the harsh fabrication process of electrospinning makes it not very suitable for cell encapsulation and bottom-up scaffold fabrication. In contrast, microfluidic spinning environment is relatively milder than electrospinning, in which most natural proteins and polysaccharides can be spun into hydrogel-based microfibers without additives. Heterogeneous materials and cell patterning in or on a single microfiber could be designed by combining sophisticated microfluidic channels in a cell-friendly environment. Therefore, microfluidic spinning is more suitable for cell encapsulation and *in vivo* immunoprotection of implanted tissues for therapeutic purposes. Basically, all tissues in the body are heterogeneous 3D structures consisting of various types of cells. Microfluidic spinning provides a powerful tool to regenerate heterogeneous 3D tissues. By weaving of various types of cell-laden fibers, 3D tissue-like structures were able to be created both *in vitro* and *in vivo*. Combining 3D printing with microfluidic spinning could also spur on innovation in tissue engineering. Incorporating a microfluidic chip head to a 3D printing system enables multi-material deposition through a single nozzle and hence avoids the alignment problem that occurs in multiple-nozzle bioprinting systems. We expect the ability to directly implant aligned cell-laden fibers that bridge gaps formed by damaged tissue will be developed in near future.

Despite numerous advantages offered by microfluidic spinning, there are still several challenges that have to be addressed. The fiber materials should be solidified within a relatively short time during microfluidic spinning. According to a specific biomedical need, the corresponding mild solidification method should also be carefully considered when a certain kind of material was selected. Until now, there are only tens of materials that have been used for microfluidic spinning, which are far from enough to meet the increasing needs of the fast developing biomedical field. Therefore, continued efforts to develop new biocompatible materials with appropriate solidification methods should be put in a priority for its practical application.

Collectively, both of electrospinning and microfluidic spinning have their own features, we should consider the fabrication processes, materials selections, fiber configurations and target applications in spinning method selection. With the rapid progress in electrospinning and microfluidic spinning, the materials (especially ECM or natural hydrogels) as well as the geometries of fiber have become considerably diverse, and their biomedical applications are rapidly expanding. Both electrospinning and microfluidic spinning methods have been developed to fabricate fibrous structures with topographical cues to direct the alignment of cells. Although the engineering of complicated tissue and organ models consisting of vascular and neuronal structures and multiple heterogeneous cells has been a great challenge, we envision the engineering of complicated organ structures will be achieved by combining spinning tools and 3D printing technology. Moreover, the combination of both spinning methods will also enable the construction of 3D scaffolds consisting of diverse fiber sizes similar to *in vivo* like ECM. Therefore, continued research and development of advanced spinning technologies will spawn a new age of tissues and organs regeneration.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.biomaterials.2016.10.040>.

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