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Biomimetic tissue regeneration using electrospun nanofibrous scaffolds

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An emerging field of tissue engineering combines medical, biological, and engineering principles to produce tissue-engineered constructs that regenerate, preserve, or slightly enhance the functions of natural tissue. By creating structures that replicate the extracellular matrix, oxygen and nutrients will be transmitted more effectively while releasing toxins during tissue repair, all while creating mature tissues. Three-dimensional nanostructures for tissue engineering have been the focus of numerous studies over the last few years. Electrospinning is a highly effective technique in this category. The last few decades, numerous nanofibrous scaffolds have been developed for tissue repair and restoration. Nanofibrous meshes as tissue engineered scaffolds for various tissues, such as neural, cardiovascular, skin, cartilage, and tendon are discussed in this article. In addition, the current article discusses recent advancements in tissue regeneration as well as challenges associated with electrospinning.

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1. Introduction

In 1959, Nobel Prize winner Richard Feynman put forward the revolutionary concept of designing molecular machines; ever since, the research community has delved further and further into the role of the various aspects of research society in what we now call nanotechnology [1, 2]. The research and application of extremely small things ‘’nano-scaler (1-100 nm)’’ is nanotechnology' [3]. In recent decades enormous progress in nanotechnology has been reported, and the recent development in nanotechnology has set very high standards in the biological and medical sciences [4, 5]. Electrospinning has gained a growing interest in the science community and industry since the late 20th century and is described a critical systematic and mercantile enterprise with worldwide commercial welfares [6]. Electrospinning is a adaptable and simple method to assemble continuous nanofibers [7]. The attractiveness of electrospinning is primarily due to the effortlessness and versatility of nanofibers' apparatus and manufacture with a high surface area to volume ratio [8].

Tissue engineering has grown rapidly in the last 30 years, giving rise to a slew of innovative treatment sessions aimed at improving on traditional methods of treating damaged living tissue [9, 10]. Defected living tissue can be repaired using this technique by utilizing some fundamental engineering, material science, and biology concepts [9]. Nanofabrication strategies enable the creation of nanofibers that strongly resembles the nanofibrous protein matrices found in natural extracellular matrix (ECM). These nanofibers have ECM-like structural and mechanical features, promoting the formation of three dimension (3D) tissue structures [11, 12]. Nanofibres tend to have a high surface area per unit volume [3], which promotes cell migration and proliferation [4].

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The tissue engineered scaffold creates the 3D plug required for the recovery and development of diseased, wounded, or defective cells, as well as the substance chosen is heavily influenced by the tissue-specific application [13]. However, regardless of the target purpose, scalable biomaterials to three dimension structures that imitate the native tissue microstructure's physiological, chemical, and physical behaviour is a major challenge [14]. These 3D nanostructured, which resemble the ECM and can be adapted with biomolecules to aid cell attachment, migrant, and propagation, can be made using electrospinning due to the relative simplicity and adaptability [4, 8].

Quite relevantly, a wide variety of polymers, both natural and synthetic with biodegradability and biocompatibility which could be reabsorbed by the human body can be electrospun [15]. These properties of electrospun nano-mesh have piqued interest of researchers in the field of medicine, leading to research into their use in neural, cardiovascular, skin, cartilage, and tendon. As a result, we will go over the most recent new techniques for making electrospun nanostructured fiber substances and using them as tissue - engineered scaffolds in this review article.

2. General electrospinning system setup and process

A syringe pump, a high voltage generator, and a collector are all essential components of the electrospinning process. An electrical field has been created by their voltage differential, as shown in Figure 1 on the syringe pump collector and needle [16]. The surface tension force and the applied electric field have the most impact on the solution drop during electrospun fiber manufacturing. A concept called as a Taylor Cone occurs when a strong electric field causes the solution to fall from a needle in a cone shape. If the electric potential overcomes the polymer solution's surface tension, the charged droplet will form a jet at the Taylor Cone's tip. Extending the jet causes a whipping motion as it passes through a thin fiber toward the collector. The instability and repelling forces generated within the jet cause it to break up into smaller fibers. As the solvent slowly evaporates into the space between the needle and the collector during this process, thin and ongoing fibers form on the collector [8, 17].

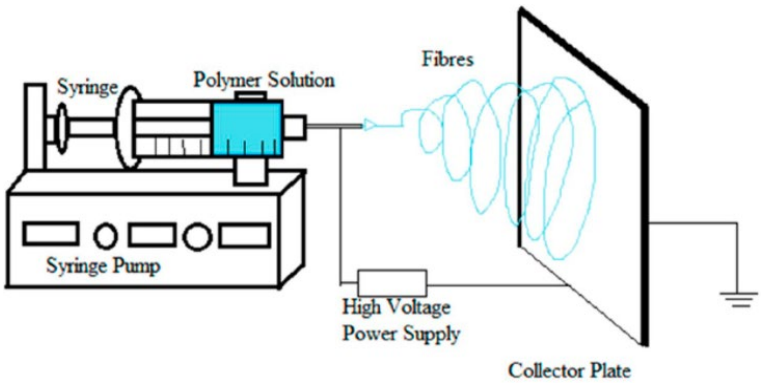

Fig. 1. The general principles and process of electrospinning.

3. Parameters influence on electrospinning process

A number of factors influence the diameter and morphology of electrospun nanofibers, including polymeric solution properties, processing parameters, and ambient conditions [18].

The morphology and diameter of electrospun nanofibers are strongly influenced by the polymeric solution properties of (such as concentration, viscosity, and the solution surface tension) [19]. The electrospinning process is heavily reliant on the concentration of the solution, hence only a minimal amount of solution is required to run the electrospinning device [20]. Nanofibrous biomaterials can only be created by electrospinning if the solution concentration is just right

during the procedure. Low-concentration solutions can result in the formation of unwanted droplets as a result of surface tension effects [21]. In addition, the high viscosity of the solution fiber structure would provide a challenge at large concentration of the material. Increases in polymer concentration may also result in fiber diameter production [22].The size and shape of the fibers can also be highly impacted by the solution's viscosity. Electrospinning requires a viscosity that is just right, so that homogeneous and fine fibers cannot be moulded in low-viscosity solutions, while a continuous jet renders generating fibers impossible in high-viscosity solutions [22, 23].

Electrostatic repulsion of surface charges and the charge density force exerted by the external field are two of the principal electrostatic forces acting on a polymeric droplet at a high voltage. Such forces cause the droplet's morphology to change from spherical to conical (Taylor cone) when the voltage hits a crucial level [24]. Electrospinning and fiber fabrication can be affected by a solvent's proper surface tension, which is a function of its nature [25]. An unsteady jet and dispersion of droplets in a solution with a high surface tension can inhibit the development of fibers [26]. At lower electric fields, electrospinning can be facilitated by decreased surface tension [27].

Electrospinning process parameters (such as applied voltage, the distance between the needle and the collector, and the flow rate of the polymer solution) are another significant category in the electrospinning fabrication process [28]. In order to produce fibrous scaffolds, the process of electrospinning must overcome a threshold voltage that creates significant charge differences in the solution [29]. The development of droplets and beads in the fibers can be varied by adjusting the voltage and, consequently, the charge quantity [30]

Polymer solution flow rate is an additional consideration in this context. The time required for solvent evaporation increases when the input rate is reduced [31]. The use of a reduced flow rate in electrospinning ensures that solvents from nanofibrous scaffolds are completely evaporated [32]. Spherical fiber diameter and shape are influenced by a variety of factors, including length between needle and collector [33]. There is a difference between fibers with big average diameter and fibers with small average diameter when the distance between the collector and the fibers is large [34]. To avoid bead formation, it is important to select an optimum concentration of solution, the voltage applied, and the distance between the tip and the collector.

Electrospun sheet fabrication requires consideration of environmental conditions such as humidity and temperature, especially when dealing with difficulty in creating homogeneous fibrous sheets. The fabrication process is slowed and charging jetting is prolonged when the humidity is considerable [35]. Humidity also has a negative correlation with the solidification time. Solvents can be eliminated completely by evaporation if the humidity is low enough, although the production of fibrils can be impaired in humid settings [36]. Nanofibrous scaffolds' morphology is also influenced by temperature. Beads, which are formed at low temperatures, and condensed and flat fibers, which are formed at high temperatures are detected [37]. Temperature increases the viscosity of the polymer solution, resulting in fibers with a smaller diameter [37].

4. Developed electrospinning methods

The traditional electrospinning could be fabricated a nanofibrous structures which determined by the shape of the collector, and the collector's angular velocity can be used to govern fiber alignment from random to precise [38].

Coaxial electrospinning, like conventional electrospinning, uses a coaxial sprayer, in which there are two different-sized spinners, one of which wraps around the other [39. The core polymeric spray is shuttled by an inner diameter smaller than the larger one, while the shell solution is transported by the nozzle with the bigger interior diameter. The case polymeric spray and the core polymeric spray, to be pumped at the same time from two distinct storage tanks, the core-shell nanofiber and the spinner is generated who used the identical process equally conventional electrospinning via the voltage differential [40, 41]. Since only the shell polymeric

spray should be electrospun in coaxial electrospinning, the electrospun biopolymers can implement non-electrospun drugs and growth factors into their core solution [42].

Emulsification electrospinning, like coaxial electrospinning, produces core-shell structure nanofibers or doing so with polymer emulsification. This method is beneficial whereas a mono spinner could indeed roll the emulsification to produce a nanofiber with several cores, without the need for an additional spinner [43]. These drops can either be resultant in nanostructure mesh to form a shape or sustain in the drops to form a multi-core architecture throughout this operation. Emulsification electrospinning might be applied to fabricate non-electrospun drugs, growth factors in polymeric solution [44].

Dynamic water flow electrospinning is a type of electrospinning in which water vortex twists nanofibers, which are then gathered on a rotary collector after being acquired on the surface of the water. An upper and lower water basin is used in this method. The water level basin has a slit in the base through that gravity turbulence could be formed on the surface of the water, if fluids flow through them. On the water's surface, the nanostructure films are first electrospun, and then drip in via vortices before even being wrapped into yarn. Using a pump, liquid and yarn are pumped from the superior watershed to the minor watershed and then back to the top watershed. Porous nano-yarn scaffold is created as the yarn streams into the minor watershed and collects on a rotary collector. Tissue engineering scaffolds made from these substances have rough surfaces, wider porosities, and higher porosities than conventional electrospun nano-meshes. This suggests that they may be better suited for 3D tissue formation [45, 46].

A different method for preparing continuous nano-yarns and involves a bi-spray of electrospun nanofibers. Single spinner generates nanofibrous mesh with positive charge by applying a high power, while another spinner generates charges with negative polarity nano-mesh by applying a negative high power. This configuration results has the effect of wrapping positively and negatively charged fibers together, which are then gathered on a rotary nozzle to shape a spiral [47].

5. Nanofibrous electrospun scaffolds for tissue engineering applications

Tissue engineered plug-scaffolds are designed to temporarily restore lost tissue by inducing tissue development and diminishment in real time as the tissue reaches maturity [9]. Since biomimetic micro-platform is constructed, resembling the native ECM's level and morphological characteristics, electrospinning has enormous potential for fabricating tissue engineering scaffolds [48]. In fact, the human body's ECM is a structural protein-based nanofibrous structure. The ECM structural fibers have a diameter of 50 to 300 nm and serve as anchoring points for cell attachment as well as maintaining overall tissue/organ shape and form [12, 49].

Electrospun nanofibers are beneficial for assembling tissue engineered nanostructures due to the versatility and tailorability of the electrospinning for the tissue - specific implementation [48]. Nanofibers can be fabricated from most biomimetic biodegradable polymers, whether used singly or in polymer meshes [15]. To direct cell adhesion and alignment within nanostructures plug, the orientation of nanofibers can be governed. This is useful for tissues with oriented ECM, such as cartilage and tendons [50].

6. Electrospun nanofibrous scaffolds for neural tissue engineering

Patients who suffer peripheral nerve damage may experience sensory, motor, or autonomic issues [51]. Peripheral nerves have a greater capacity for regeneration than the central nervous system [52]. It is necessary to use biodegradable polymers to keep the two ends of the injured nerve together so that restoration can take place in cases where the nerve damage is longer than 5 millimeters [53]. As a result of these investigations, materials developed from plain hollow fibers

to nerve guidance conduits, which are more complicated still, which use electrospinning to create neural scaffolds [54].

Wang group [55] created a nerve guidance conduit by electrospinning a silk fibroin scaffold and P(LLA-CL) mixed aligned nanofiber scaffold, then twisting it around a metal rod to create a silk fibroin scaffold. For the purpose of evaluating nerve regeneration, the nerve guidance conduit with 10-mm nerve root wound was treated with a biocompatible implant. in rats. Herein, the nerve guidance conduit enhanced restoration, resulting in a more level headed nerve with thicker nerve fibers and a higher density than the fabricated control nerve.

According to Zhang et al [56], to improve nerve regeneration, nerve guidance conduits were created using aligned electrospun fibers and coaxial electrospinning. In that study nerve guidance conduit was gradually released from the electrospun scaffold and the ability to maintain activity for long-term recovering success necessitates treatment for at least 60 days. Furthermore, after a 12-week *in vivo* model, the nerve guidance conduit -containing scaffold outperformed the control.

Wang et al. [57] looked into the use of nerve guidance conduit in the core of poly(lactic-co-glycolic acid) nerve guidance conduit was made from shell fibers aligned in configuration, enclosed with nylon nozzle after being rolled around a steel rod (Figure 2). The scaffold prompted regeneration Sciatic nerve wound in rats with a 13-mm diameter was treated with growth factors for 85 days, and research into electrophysiology and tissue mass demonstrates that the reconstructed nerve had fully recovered its previous function was notably greater than the non-growth factor control.

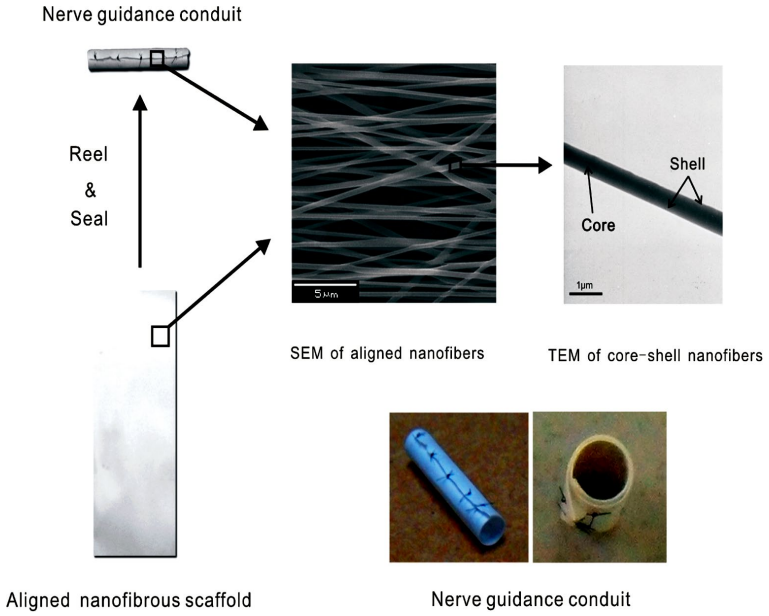

Fig. 2. A diagram depicting the alignment of the core–shell nerve guidance conduit (NGC). The aligned PLGA/NGF nanofibrous scaffolds were wound onto a stainless steel bar and stitched shut with 8-0 nylon monofilament sutures. The nanofibres were oriented parallel to the axis. So that an aligned NGC could be obtained, the steel bar had to be bent. The PLGA/NGF was 14 mm long and had an inner diameter of 1.4 mm and a wall thickness of 0.3 mm.

According to Zhang et al. [58], coaxial electrospinning was used to create a composite fiber scaffold containing polyaniline for conduction as well as nerve guidance conduit, and the researchers then tested the synergistic effects of electrical stimulation and nerve guidance conduit on tissue regeneration. Nerve guidance conduit stimulated Schwann cell proliferation as well as the development of pheochromocytoma cells have developed new long axonal plugins, indicating that the overall impacts are advantageous for neural tissue repair.

A nano-yarn-filled nerve guidance conduit was made from electrospun poly (lactic-co-glycolic acid) and coated with laminin to improve cell adhesion by Wu et al. [59]. Neurovascular recovery is controlled and enhanced by bio-signals as well as topographies, as demonstrated by *in vitro* models that showed the laminin membrane accelerated the cell migration and invasion of Schwann cells.

Using electrospun polycaprolactone nano-yarn filaments coated with polypyrrole to make a capacitive, microtubule circuit nerve guidance conduit was another study. Large pores and high porosity were achieved by electrospinning a nanofiber sponge, as described by Sun et al. [60]. Nerve guidance conduit sponge was managed to infiltrate for 10-mm sciatic nerve defects, the inner configuration of the nerve package was embedded in rats with Schwann cells, according to histological analysis. Sponge-filled scaffold outperformed a control with muscle weight and motion analysis when compared to a hollow nerve guidance conduit in fully functioning nerve recovery.

7. Electrospun nanofibrous scaffolds for cardiovascular tissue engineering

In order to direct blood vessel recovery, many biomedical researchers team is currently working on electrospun nano-structurer meshes, absorbable slight span vascular grafts and avoid drawbacks of conventional synthetic grafts [61].

There has been research on heparin and anticoagulants growth factor in the order to help decrease clotting and improving the function of the endothelium [62]. Huang et al. [63] adopted coaxial electrostatic spinning create a heparin-containing electrospun poly (P (LLA-CL) fibrous graft from poly (L-lactic acid-co-caprolactone). Heparin, when injected in a dog's femoral artery, enhanced legibility by acting as a blood thinner. Towards encourage endothelial progenitor cells to proliferate. Chen et al. [64] employed emulsion electrospinning to load vascular endothelial growth factor into the heparin-containing scaffold. Heparin and VEGF released by vascular grafts were considered to have excellent anticoagulant properties and to enhance endothelial progenitor cell proliferation. Collagen and chitosan were combined with P(LLA-CL) by Yin et al. [65]. When collagen and chitosan were added to the P (LLA-CL) control, endothelial cell proliferation and spreading increased considerably, implying improved cytocompatibility. Kuang et al. [66] exploited coaxial electrospinning with heparin-loaded silica nanoparticles and salvianolic acid B-loaded outer shell to prepare the inner layer of an electrospun vascular graft. The discharge of heparin and SAB was prolonged for about 4 weeks, and the two factors worked together to increase endothelial cells isolated from the umbilical vein of the umbilical cord development and blood compatible. Wu et al. [67] prepared nanoyarns using dynamic liquid electrospinning and 75 % P (LLA-CL) and 25 % collagen are used in covalently electrospinning to generate nanoyarns. This study found that flexible nanoyarns controlled vascular smooth muscle infiltrate while coupled nanoyarns steered cell growth in a specific direction. This suggests the use of both nanostructures in the healing of tunica media. Wu et al. [68] created a tightly packed nanofiber in which inner layer helps prevent transmural blood leakage and a loose nanoyarn outer layer helps direct vascular smooth muscle regeneration (Figure 3). Similarly, to promote endothelial cell adhesion, heparin and CD133 antibodies were coaxially electrospun into an electrospun scaffold's inner layer, which was then encased by a dynamic liquid electrospinning-generated upper shell of nanoyarns. A second study found that when heparin and CD133 were assimilated in a rat's abdominal aorta for two months, the cells in the monolayer regenerated and smooth muscle cells infiltrated.

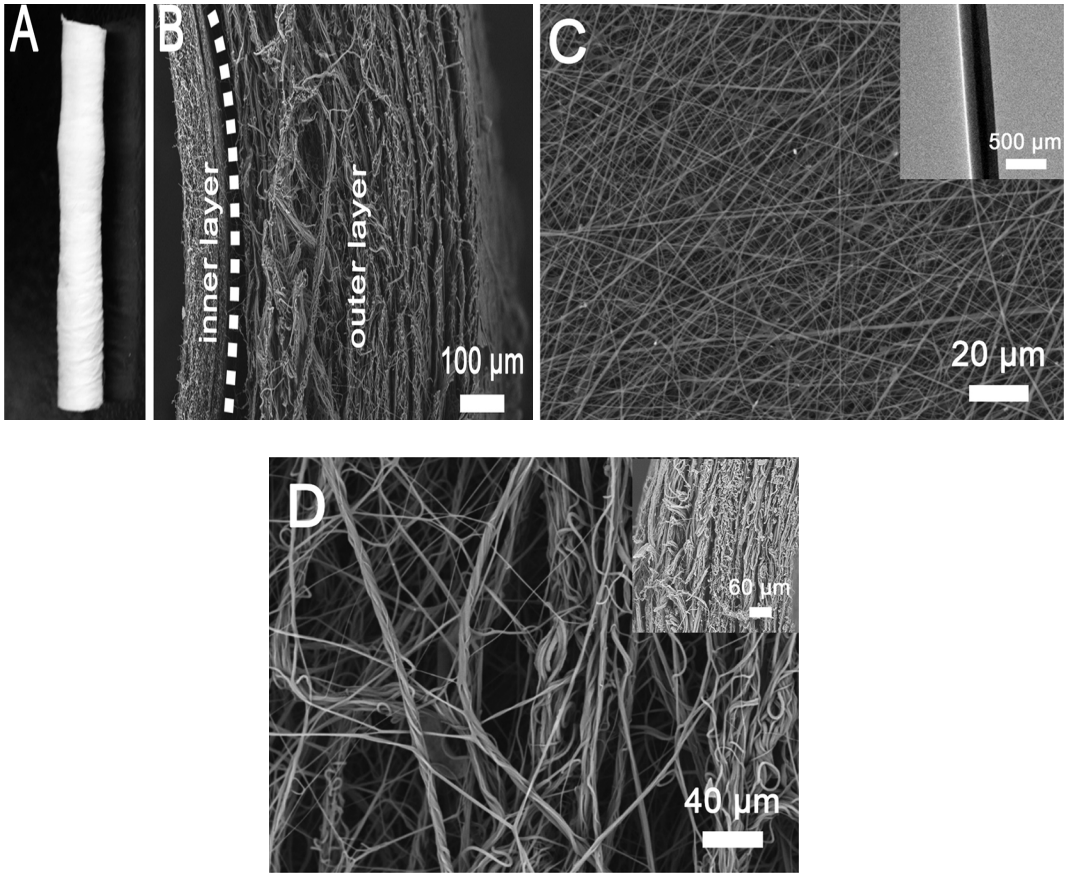

Fig. 3. (A) Image and (B) SEM micrograph of the bilayer vascular scaffold cross section. (C,D) SEM micrographs of the surface of the bilayer vascular scaffold's inner and outer layers; TEM micrograph inset in (C) was a single PLCL/COL-HEP/CD133 nanofiber; SEM micrograph inset in (D) was a cross section of the PLCL/COL nanofiber yarns.

Tondnevis et al. [69] introduced that gelatin and mono-walled carbon nanotube were used with polyurethane nanofibers that are physio-chemically and biologically moldable can help regenerate the heart after an attack. Composite scaffolds with biomimetic physical behavior, such as blood vessels, have been created and their Young modulus and ultimate strength managed to improve. Seven days of culture yielded the closely packed and confluent sheet of nanofibrous surface was protected by a thick layer of myocardial myoblast and endothelial cells, which is critical for cardiovascular tissue engineering. After the experiments were completed, it was determined that the fabricated scaffolds were suitable for cardiovascular tissue engineering applications. Ahmadi et al. [70] fabricated structurally imitate the extracellular matrix of cardiac tissue using a variation of polyurethane - chitosan and the random and the aligned direction of the carbon nanotube electrospun nanofibers. Nanofibrous scaffolds electrospun randomly and aligned were found to be biocompatible and viable when used with H9C2 cells. The results showed that the fabricated nanofibrous composite scaffolds were nanoscale electro-conductivity and aligned nanofibers are both emerging characteristics for the healing of infarcted myocardium in scaffolds with them.

8. Electrospun nanofibrous scaffolds for skin tissue engineering

Largest organ in the body is the skin, and it serves as a protective barrier against pathogens [71]. A common method for speeding up wound healing is autologous skin grafts, but this can lead to side effects and complications depending on the degree of tissue damage, donation may not be an alternative [72]. Another option is to guide healing and provide protection using a tissue

engineering scaffold [73]. The scaffold's additional functions include keeping the wound moist, adsorbing secretions, having good air permeability, and preventing bacterial growth around it [74]. As a result, the advantages of electrospun scaffolds for skin tissue regeneration make them an attractive option [75].

In *vivo* model, Zhang et al. [76 used a silk fibroin-antimicrobial an electrospun nanofiber mesh containing a peptide matrix with substantial antibacterial properties, as well as a faster rate of wound healing. When Li et al. [77] formed nanofibers from tilapia skin collagen using electrospinning, they found that the membranes were both biocompatible and immunogenic; indicating that tilapia skin collagen could be an excellent basis of collagen for skin tissue engineering projects and the development of a hemostatic biomaterial is the priority.

Bioactive glass was integrated into nanofibers made from electrospun fish collagen to enhance the electrospun biomaterial's physical behavior [78]. In comparison to the nanocomposite made from pure fish collagen control nanofibers had better ultimate strength, antimicrobial contrary to Staphylococcus aureus, and encouraged the migration and growth of skin fibroblasts. Xie et al. [79] developed an electrospun nanofibrous plug using five O-quaternary ammonium chitosan, which is highly effective against bacteria, and showed that it was compatible with plasma and biocompatible, repressed wound healing was accelerated by the configuration of a hemostatic biofilm. Using electrospinning, mechanical cutting/mincing, freeze drying, and heat treatment, Yu et al. [80] have established a four-step process for fabricating an improved porosity and adsorption scaffold. With its large pores and high porosity, the scaffold made of polyethylene glycol and polycaprolactone, on the other hand, absorbed 3.3 times more water than a two-dimensional lipid bilayer.

Narayanan et al, [81] explored that the extracellular matrix can be mimicked for skin tissue engineering by using electrospun nanofibers of glucose-reduced graphene oxide that were chemically crosslinked with acidic glutaraldehyde and enhanced with polyvinyl alcohol scaffolds. In *vitro* hemolytic, viability and proliferation assays with CCD-986Sk (a human skin fibroblast cell line), and live/dead cell imaging were used to evaluate the biological activities of nanofibrous scaffolds. In addition, the nanofibrous scaffolds was extremely well-tolerated by fibroblasts, and its metabolism increased dramatically. The nanofibrous scaffolds increased fibroblast proliferation and viability in the presence of DAPI staining and live/dead imaging assays, leading to the possibility of skin tissue engineering. Jiang et al, [82] fabricated sandwich scaffold mimics the strain-strengthening activity of individual tissues. To begin, we use wet electrospinning to create polycaprolactone yarns. After that, we'll make a textile out of polycaprolactone yarns crocheted together. Finally, the sandwich scaffold is built by sandwiching the textile fabric between two electrospun mats.

By using wet electrospun polycaprolactone yarns, you can induce cell alignment and lengthening in your research animals. The textile-based sandwich scaffold exhibits tensile-strengthening properties. After optimizing the thickness of the sandwich scaffold's outermost layer, the scaffold is also capable of supporting cell proliferation and infiltration. Textile-based sandwich scaffolds have the ability to mimic the physical, mechanical, and biological properties of human skin and other tissues, according to the findings of this study.

9. Electrospun nanofibrous scaffolds for tendon tissue engineering

The most common type of tendon injury is a rupture or tear, which can cause excruciating agony and necessitate up to 50 million surgical procedures per year [83, 84]. There is currently a viable approach for treating and regenerating injured tendons using tissue engineering scaffolds made of electrospun fibers [85].

Yang et al. [86] have produced an innovative, multiple-layered PCL/methacrylated gelatin composite scaffold with human adipose stem cell interspersions and double electrospinning (Figure 4). A methacrylated gelatin layer encased in five sheets of crosslinked polyethylene reinforced the scaffold. For 7 days, the human adipose stem cells were added with TGF-3 to

encourage differentiation into tenocytes, and protein production assay revealed a significant increase in the expression of the tendon markers scleraxis and tenascin-C.

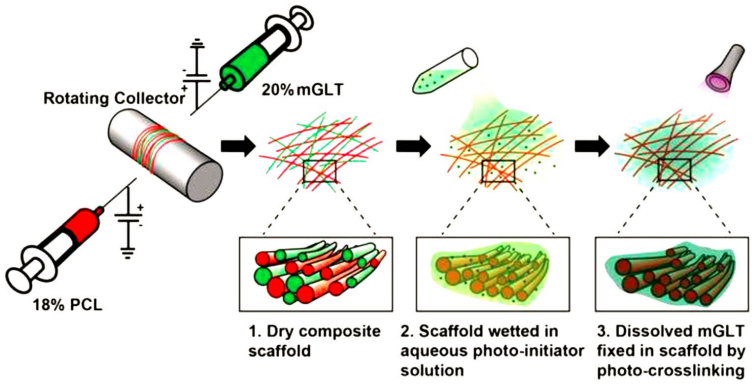

Fig. 4. Preparetion of the composite scaffolding. A scaffold made of PCL and mGLT fibers was constructed using dual electrospinning. After soaking the dry scaffold in aqueous photo-initiator solution, visible light (VL) photocrosslinked it to keep the gelatin in place.

Gelatin and PCL nanofibrous scaffolds combine to create a new cell-scaffold construct that mimics the mechanical properties and structure of tendons while also helping to promote the natural tendon cell. The electrospun nanocomposite technique developed by Rinoldi et al. [87] was used to construct tendon tissues. Bead-on-string fiber structures were developed and silica particles were added to adjust the constructs' topography, wettability, stiffness, and degradation rate in terms of improving their bioactivity. Those research' findings suggest that the fibrous nonwoven nanocomposite bead-on-string scaffold could be a promising option for directed tendon healing.

After extensive testing, it was discovered that while the scaffolding did not exhibit conventional plastic deformation in high strain, it resembled the nonlinear deformation performance of tendons. Human adipose-derived stem cells differentiated into a tenogenic-like phenotype after being exposed to the scaffolds, which increased the amount of ECM deposited by the cells. The scaffolds' stress-strain curves resembled tendons characteristic nonlinear deformation behavior, but lacked the normal plastic deformation seen in tendons under high strain. Human adipose-derived stem cells differentiated into a tenogenic-like phenotype after being exposed to the scaffolds, which increased the amount of ECM deposited in the tissue [88].

A histone deacetylase inhibitor, trichostatin A, was electrospun into a scaffold by Zhang et al. [89] and tested for its effect on tenocyte development. The effects of trichostatin were greater in comparison to those of controls that did not use either the signaling molecule or random PLLA nano-platforms. A significantly increased the expression of tendon markers and this study suggests that using trichostatin and topographical cues from aligned fibers could help promote teno-lineage differentiation and repair of tendon defects. In order to create a tendon-to-bone interface, researchers used an electrospun mesh.

Perikamana et al. [90] immobilized PDGF-BB on its aligned fibers in a curves on its platelet-derived growth factor encourage adipogenic stem cell tenogenic development. PDGF-BB gradients on aligned nanofibers worked in concert with topographical signals to spatially govern cell differentiation, resulting in an anisotropic structure similar to the tendon-bone insertion site with lengthy cytoskeletons. These findings support the hypothesis. A 14-day study revealed that the scaffold enhanced the levels of biomarkers of tendon formation. According to these findings, a PDGF-BB gradient on aligned nanofibers could be effective for engineering the bone-tendon junction. Bone-tendon engineering may be improved by using aligned nanofibers coated with a PDGF-BB gradient.

PLLA and PLLA layers filled with nano-hydroxyapatite were used by Li et al. [91] to create a double-layer scaffold that mimicked enthesis fibrocartilage mineralized and non-mineralized. In an in *vivo* research, the plug dramatically improvement in collagen structure and an

increase in glycosaminoglycan staining at the tendon-bone interface in comparison to an electrospun polylactic acid. Based on study findings, the bi-layered scaffold may be useful for tissue engineering because it allows for precise control over the location of repaired at the tendon-bone interface, mineralization and non-mineralization.

10. Electrospun nanofibrous scaffolds for cartilage tissue Engineering

Injuries to the articular cartilage caused by sports, trauma, and old age can lead to osteoarthritis and crippling joint pain, possibly requiring joint replacement surgeries [92, 93]. It's important to develop new methods for fabricating electrospun 3D nanofibrous scaffolds appropriate for cartilage regeneration and replicating the natural ECM for minimal and serious cartilage defects to minimize the incidence of osteoarthritis and total joint replacement [94, 95].

Hyaluronic acid and polyethylene oxide solution-electrospun poly Lactic-co-Glycolic Acid /gelatin nanofibers from a finely diced layer have been established by Chen et al [96]. Water-induced shape memory and high porosity were discovered in the hydrophilic scaffold, which was found to have a large number of regular pores between the fibers and a high porosity. Since the 3D printable scaffold returns to its original form within 30 seconds, it indicates that it could be used to guide *in vivo* cartilage tissue engineering.

In order to repair an osteochondral defect, Zhang et al. [97] used a double layered scaffold made of electrospun polylactic acid nanofibers and compressed type I collagen. The bi-layer scaffold outperformed a collagen-only control *in vitro* and *in vivo*, promoting osteogenic differentiation and inducing rapid subchondral bone formation were studied in rabbit's models. Wang et al. [98] created a new core-shell P (LLA-CL)/collagen nanofiber scaffold by adding bovine serum albumin and recombinant TGF-3 to the core. Over a two-month period, the TGF-3 was released, and type II collagen and aggrecan secretion by chondrocytes showed it to be bioactive. Additional research has shown that seeding mesenchymal stem cells from Wharton's jelly onto the scaffolds increased cell proliferation and morphological assessments as well as chondrogenic differentiation.

Irani et al. [99] designed a nanofibrous scaffold based gelatin/polyvinyl alcohol/chondroitin sulfate for cartilage regeneration by enhancing mesenchymal stem cells chondrogenesis differentiation on fabricated nanofibrous scaffold. After carrying out a cell viability assay, researchers discovered that the mesenchymal stem cells adhered and survived better to the nanofibrous scaffold, and that the chondrogenic markers collagen type II and chondrogenic proteoglycan also performed better. The fabricated nanofibrous scaffold nanofiber appears to be a promising material for cartilage tissue engineering, according to this research. Shojarazavi et al. [100] fabricated an electrospun nanofibrous silk fibroin combined with alginate/cartilage extracellular matrix hydrogel for cartilage tissue regeneration. The results showed that increasing the alginate concentration enhanced the compression elastic properties, as well as water retention potential, degradability, cell viability, and aggrecan and collagen type II synthesis for the best hydrogel to promote its possibility as a proposed nanocomposite scaffold for cartilage injury regeneration. Chen et al. [101] designed a novel 3D porous electrospun polylactic acid combined with gelatin/ chondroitin sulfate scaffold for cartilage tissue regeneration. *In vivo*, rabbit cartilage defects were created and the chondrogenic potential for fabricated nanocomposite scaffold was enhance and the chondrogenic markers collagen type II and chondrogenic proteoglycan was expressively improved. Even so, notable reductions in two essential inflammatory factors in fabricated nanocomposite scaffold confirmed inflammatory inhibitory activity, indicating the favored property of fabricated nanocomposite scaffold for cartilage tissue engineering and its immuno-regulation ability.

11. Electrospun nanofibrous scaffolds for bone tissue engineering

The number and variety of tissues that can be grown using tissue engineering is endless, however there are factors that researchers have to put into consideration in order to ensure the growth of the cells or tissues [102, 103]. Engineers and researchers designing the scaffolds have priorities such as the bio compatibility which is rather referred to as step one. Then comes the factor of the scaffolds being biodegradable. The scaffold must have the feature of degrading with time after being successfully delivered to the subject [104, 105]. Since this is bone tissue engineering, factors such as durability of the scaffold to remain intact upon delivery must be considered as well; therefore the scaffold must be able to withstand ambient pressure until the cells fuse. Nevertheless, it is important that the scaffold has a high surface area that will enable the size of the scaffold to be as minimal as required [105-107]. There are many polymers that can be chosen for the manufacturing of scaffolds depending on the location of the implantation and the type of tissue grown. Polymers have the factors mentioned to successfully grow the desired bone or tissue; biomaterials that are most common to be used in bone tissue engineering are chitosan, alginate, collagen and other polymers such as polylactic acid and polyglycolic acid [103, 108]. Especially when it comes to bone tissue engineering concerning scaffolds, researchers and engineers keep in mind biocompatibility, biodegradability and rigidity. The scaffolds constructed must have those features when growing either bones or cartilage since their functions in the body is mainly support and structure, the struggle is with both the growing and implantation [109, 110]. Bone tissue engineering concerning at scaffolds provides proliferation and cell attachment, which then leads to bone formation [103]. Rajzer and colleagues came up with an astonishing method where they showed that calcium phosphate osteogenic nano particles can be used in enhancing the scaffolds to grow bone tissue more efficiently by injecting polyaniline using an inkjet, the scaffold can be printed to improve the tissue growth [111]. Another study used hydroxyapatite due to its properties being close to the minerals of the bone; however, its fabrication with the nano fibrous scaffold also contained bone morphogenetic protein 2 and silk fibroins, and using this method and scaffold able to culture mesenchymal stem cells in constant condition for 31 days, furthermore the stem cells differentiated towards osteogenesis [112]. Samadian et al, 2020 fabricated a new electrospun nanofibrous osteoconductive carbon with hydroxyapatite particles to be used *in vivo* as the scaffold for bone tissue engineering. The osteoconductive properties of the proposed nanocomposite considerably enhanced *in vivo* bone growth in the rat's femur damaged tissue. Furthermore, histological results revealed that the nanocomposite treated group had meaningfully more bone regeneration than the damage without treatment. The results showed that the proposed fabricated nanocomposite was a potential material for bone regeneration [113]. Preeth et al. 2021 introduced a bioactive Zinc composite combined with polycaprolactone/gelatin electrospun nanofiber to boost bone tissue regeneration. Zinc is a trace mineral that is required for normal bone formation and has been shown to enhance bone formation The authors showed that the nanofibrous mesh with zinc was biocompatible *in vivo* with high osteogenic markers expression and can be used as a therapeutic agent to repair bone defects and enhance bone formation [114]. In another study, Meka et al., 2019 introduced a new modified in situ sol-gel approach to create a unique multi-component PCL nanofibrous scaffold including bioactive ceramic particles. The scaffolds improved hMSC osteogenic differentiation and HUVEC angiogenic activity. These findings show that such polymer/ceramic nanofibrous scaffolds have multibiofunctional properties and are thus viable options for bone tissue regeneration scaffolds [115].

Conclusions

The use of cutting-edge nanomaterials in combination with improved engineering techniques casts a positive light on tissue regeneration research. Electrospinning is a powerful tool for creating a wide range of nanostructured fibers because of its versatility and attractiveness. Materials with various morphological properties have been combined with it in a variety of ways for tissue engineering, including:

The ECM nanostructure is more closely resembled by electrospun nanofibrous structures than by other conventional methods. These cutting-edge nanofibrous scaffolds have been proven in numerous studies to work. There is still work to be done to fully define previously manufactured micro- and nano-scale fibers, both *in vitro* and in vivo Researchers should focus on specific scaffold uses by fine-tuning system functions to replicate the defined target cells and tissues rather than consider designed nanofibrous scaffolds for biomedical technologies as a general concept.

Enhancing the mechanical behavior of electrospun nanostructures was necessary, and tissue engineers are currently facing a significant challenge in doing so. This has led scientists to investigate polymer-ceramic composite fibers and thermal treatments to improve fiber bonding, and 3D scaffolds with layered materials may be required.

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