

Piezoelectric nanofibers as biomaterials for bone regeneration and wound healing

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Abstract

Piezoelectric properties of materials are becoming a more relevant area of research for biomaterials. Examples of these materials are polyvinylidene fluoride (PVDF), collagen, and a combination of these with other materials like polycaprolactones (PCL) and multi-walled carbon nanotubes (MWCNT). These materials offer the unique ability to respond to an applied electric field with a mechanical response or vice versa, with an electric response to an applied mechanical force. This behavior can be instrumental in modern medicine for wound healing and bone regeneration. A variety of cells (osteoblasts, epithelial cells, mesenchymal cells) have all shown piezoelectric properties. This would allow for the use of piezoelectric materials to aid in cell migration, proliferation, and differentiation, facilitating the end goal of wound healing and bone regeneration.

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1. Introduction

The field of biomaterials is rapidly expanding as new advancements in materials science are investigated and developed. The use of piezoelectric materials and devices is one of the areas pushing advancement in biomaterials. The simple and reversible energy transfer of mechanical to electrical energy opens a litany of options in modern medicine. Advancements in tissue engineering and biomedicine offer great potential in piezoelectric nanofibers as a part of scaffold material. A clear application for this property is wound healing and tissue regeneration [3]. Ultimately the behavior of the cells involved in healing dictates the approaches in helping this process. This includes cell migration, proliferation, and adhesion, all of which have been found to respond to electrical stimulation [3]. The use of piezoelectric nanofibers can create and maintain electric fields around areas of wounds, expediting the healing process [4]. Quicker wound healing process with directed cell migration and adhesion with applied electric fields has the potential to revolutionize tissue engineering and regenerative medicine. PVDF/PCL, collagen, and PVDF/MWCNT are

reviewed in their ability to aid in wound healing and bone repair.

Biocompatibility and integration of all biomaterials must be considered. There are a number of piezoelectric materials that occur naturally and are researched. Bone is an example of naturally occurring piezoelectric material. Collagen is a piezoelectric nanofiber that occurs naturally in the human body and can be synthesized through processes such as electrospinning [11]. Other areas of research investigate artificial piezoelectric nanofiber scaffolds, like PCL/PVDF which demonstrates good biocompatibility and better mechanical properties than collagen (especially when paired with chitosan). PVDF will be investigated in the β phase, as it is the only phase exhibiting a dipole moment which allows for piezoelectric properties. Carbon nanofibers have been synthesized as the substrate for bone cell electrical stimulation which complement the piezoelectric properties of bone [11]. Though the fabricated nanofibers do not exhibit piezoelectric properties, they can be used in combination with bone and other fibers to attain the desired result.

Electrospinning is used to synthesize all of the nanofibers that have been introduced. It is a consistent method to synthesize aligned nanofibers and is a relatively cheap

processing technique. Aligned nanofibers have good mechanical and electrical properties; both are highly sought in tissue engineering and regenerative medicine [8]. In short, electrospinning nanofibers applies a high voltage to a polymer solution in a syringe and then distributes the charged solution across charged electrodes resulting in aligned nanofibers [7]. These properties can be specified through changes in applied voltage, concentration of polymer solution, distance between electrodes, distance from syringe to electrodes, and others.

This review will detail the synthesis and application of nanofibers and the piezoelectric properties they exhibit for the purpose of wound healing and tissue regeneration. These nanofibers investigated are PVDF/PCL, collagen and PVDF/MWCNT.

2. PCL/PVDF

PVDF/PCL is a versatile nanofiber-based scaffold that plays a large role in modern advancements in tissue engineering. Before investigating the piezoelectric properties of PVDF/PCL, the biocompatibility of these fibers must be suitable. PVDF/PCL alone demonstrates good biocompatibility and is evident through cytotoxic and adhesive tests. PVDF when left alone does not demonstrate good biocompatibility; however, the combination with PCL assists this factor. PCL has shown great long-term biodegradation; PCL breaks down into small, non-toxic products through simple hydrolysis [1]. This makes PCL a good contender for long term implant materials and controlled release applications [1]. This includes tissue regeneration. PCL has also been used in combination with barium titanate nanoparticles to improve mechanical and piezoelectric properties [1]. Rat Schwann cells have shown increased proliferation and protuberances on barium titanate doped PCL scaffolds. The mechanical properties have also been tested in contact with Rat Schwann cells. Incisions (two 1 cm long incisions) were made on posterior flanks of male Sprague-Dawley rats [2]. The left side was provided PCL tissue scaffold material and the right side was not. The wounds were sutured and observed for 14 days. The areas treated with PCL scaffold demonstrated less inflammation and less scarring than the areas left untreated [2]. The long-term and immediate responses in wound healing were investigated and shown to have overall positive impacts on the process while remaining biocompatible.

PVDF demonstrates good piezoelectric properties and is integral in modern biomaterial devices. Piezoelectric polymers have outperformed many piezoelectric ceramics; brittleness of ceramics limits the application in tissue engineering when large load is a factor. The piezoelectricity of PVDF arises from the difference in electronegativity between the fluorine and the hydrogen ions, creating a dipole moment from fluorine to hydrogen [3]. Piezoelectricity of a material is largely dependent on two factors: material permittivity and piezoelectric coefficient [3]. The piezoelectric coefficient can be increased for PVDF by annealing at 135°C (above Curie temperature of 113°C) and below the melting temperature (147°C) [5]. Reis et al investigated Li-ion battery powered PVDF actuators for

electrical stimulation healing of fractured bone. The designed actuators accumulation dramatically increased the amount of bone on the surface of the PVDF scaffold compared to static controls [4]. One common concern cited in Reis et al and Kapat et al questioned the biocompatibility of PVDF [3, 4]. The biodegradation of PVDF can release harmful toxins into their environment, however, the complementary use of PCL in the scaffold lessens this threat drastically [1]. Fabricating PVDF/PCL substrates with increased piezoelectric coefficients from annealing temperature has shown good results in the process of bone fracture healing.

3. Collagen

Collagen nanofibers are excellent bone scaffold materials due to their biocompatibility and osteoconductivity. They function notably well in regenerative tissue engineering when combined with hydroxyapatite to form porous composite scaffolds with good mechanical properties [9]. Modern research has augmented collagen scaffolds to include growth factors conducive to healing large bone defects [9]. Walsh et al. successfully fabricated collagen-hydroxyapatite scaffolds that acted as carriers for growth factors (GF), leading to rapid defect bridging [9]. Collagen is the primary contributor to the piezoelectricity of bone, although collagen's hierarchical nature makes it difficult to isolate smaller structures to determine the underlying piezoelectric mechanism [10]. It is known that electrical stimulation aids in bone healing, but current research is focused on understanding collagen's electromechanical properties at different scales to increase the potential for future use. Recent research has used piezoresponse force microscopy (PFM) to determine a piezoelectric tensor at the nanoscale, holding implications for collagen nanofibers [10]. Denning et al. harvested tendon from a rat and performed PFM on the rat collagen samples oriented at different angles, finding the piezoelectric tensor on the same scale as individual collagen fibrils. They found the average local piezoelectric coefficient to be on the order of 1pm/V , and dependent upon fibril orientation.

These results are beneficial in that they confirm the importance of fibril orientation on macroscopic piezoelectric properties, having potential influence in future structures of regenerative bone biomaterials.

4. Carbon Nanofibers in Bone Scaffolds

Carbon materials are biocompatible with bone tissue, offering a potential material for bone repair and regeneration. Carbon materials in the form of nanofibers and nanotubes create a 3D scaffold serving as the base, with the help of tissue cells and biological cues, for bone regeneration [6]. Carbon nanotubes in particular are well suited for this application due to their excellent mechanical properties as well as directionally dependent thermal and electrical properties. These properties allow for a small inclusion of CNTs into the overall matrix to create a strong, biocompatible composite through cheap manufacturing techniques such as electrospinning [6].

Carbon nanofibers and nanotubes have also been investigated in healing bone fracture and aiding in muscle

recovery. Electrospun carbon nanofibers were fabricated with polyacrylonitrile nanofibers as a precursor in a study conducted by Samadian et al [7]. These carbon nanofibers had a DC field stimulus applied to the CNTs to examine the electrical response. With the introduction of the CNTs into the electric field, the current density altered from homogeneous (absence of CNTs) to direct increase in current density through the CNTs [7]. This demonstrates the ability of CNTs to direct and increase current density when in presence of an electric field. CNTs can be fabricated in conjunction with PVDF to create a scaffold with great electric and mechanical properties. Commercial PVDF has a piezoelectric strain constant of -15 pm/V where PVDF/MWCNT have a constant of -56 pm/V [11]. The increase in electrical properties is clear; however, the mechanical properties are also favored. Adding 0.03 wt.% of MWCNT to the PVDF nanofibers increased the Young's modulus from 0.26 GPa to 0.31 GPa, a 19% increase [11]. PLA/MWCNTs nanofiber composites have demonstrated their ability to promote osteoblast growth with both random and aligned orientations and electrical stimulation generating osteoblasts with aspect ratios as high as 7-9 [6]. Carbon nanotubes offer a highly versatile and strong addition to bone regeneration scaffolds which can further promote osteoblast growth by utilizing the electrical properties of CNTs.

5. Conclusions

Nanofiber piezoelectric biomaterials offer a promising avenue for wound healing and regeneration of naturally piezoelectric materials such as bone. The movement of cells is the limiting factor in the healing process which this technology addresses on multiple fronts. Incorporating these nanofiber materials, with the addition of electrical stimulation, can aid in cell migration, proliferation and adhesion, ultimately speeding up the healing process. These materials can be included to existing bone scaffold technology at very low concentrations, on the order of hundredths of a weight percent in some systems, to see significant improvements to healing rates with the addition of electrical stimulation. These materials can also offer improvements in regard to mechanical, thermal and electrical properties, especially in the case of MWCNTs improving durability and piezoelectric ability of the scaffolds. Furthermore, electrospinning can be used which is relatively inexpensive and simple to create high quality, aligned nanofibers. Overall, aligned piezoelectric nanofibers improve many aspects of bone regeneration and healing with multiple promising material systems.

6. Discussion/Future Directions

Small inclusion of CNTs are used to improve the electrical and mechanical properties of nanofibers and tissue scaffolds. It was found that doping PVDF scaffold with CNT at 0.05 wt.% lead to beads arising (clumps of fibers rather than the intended aligned nanofibers) and lack of fibers synthesized [7]. One area of future research would investigate increasing

this percentage to increase the mechanical and physical properties of the scaffold. Additionally, the inclusion of PCL, collagen, or other nanofibers combined with CNTs could increase performance and biocompatibility of future scaffolds. [8]

The biocompatibility of PVDF nanofibers remains a concern. The uncontrolled release of harmful products from the nanofibers could impose serious health risks to the patient in the long term. In addition to finding plausible supplementary nanofibers to further mechanical and electrical properties of PVDF, the biocompatibility must also be investigated. The use of PCL, discussed previously, can reduce the effect; however, release of harmful products of PVDF remains a threat. Finding more suitable and reliable methods to increase the biocompatibility of PVDF should also be investigated.

Conflict of Interest

No conflict of interest to be declared.

References

- [1] Cheng, Y., Xu, Y., Qian, Y., Chen, X., Ouyang, Y., & Yuan, W. E. (2020). "3D structured self-powered PVDF/PCL scaffolds for peripheral nerve regeneration". *Nano Energy*, 69, 104411.
- [2] Zhang, W., Ji, T., Lyon, S., Mehta, M., Zheng, Y., Deng, X., ... & Kohane, D. S. (2020). Functionalized Multiarmed Polycaprolactones as Biocompatible Tissue Adhesives. *ACS Applied Materials & Interfaces*, 12 (15), 17314-17320.
- [3] Kapat, K., Shubhra, Q. T., Zhou, M., & Leeuwenburgh, S. (2020). "Piezoelectric Nano-Biomaterials for Biomedicine and Tissue Regeneration". *Advanced Functional Materials*, 1909045.
- [4] Reis, J., Frias, C., Canto e Castro, C., Botelho, M. L., Marques, A. T., Simões, J. A. O., ... & Potes, J. (2012). A new piezoelectric actuator induces bone formation in vivo: a preliminary study. *BioMed Research International*, 2012.
- [5] Ribeiro, C., Pärssinen, J., Sencadas, V., Correia, V., Miettinen, S., Hytönen, V. P., & Lanceros-Méndez, S. (2015). Dynamic piezoelectric stimulation enhances osteogenic differentiation of human adipose stem cells. *Journal of Biomedical Materials Research Part A*, 103 (6), 2172-2175.
- [6] Shao, S., Zhou, S., Li, L., Li, J., Luo, C., Wang, J., ... & Weng, J. (2011). Osteoblast function on electrically conductive electrospun PLA/MWCNTs nanofibers. *Biomaterials*, 32(11), 2821-2833.
- [7] Samadian, H., Mobasheri, H., Hasanpour, S., Ai, J., Azamie, M., & Faridi-Majidi, R. (2020). Electro-conductive carbon nanofibers as the promising interfacial biomaterials for bone tissue engineering. *Journal of Molecular Liquids*, 298, 112021.
- [8] Dong, R., Ma, P. X., & Guo, B. (2020). Conductive biomaterials for muscle tissue engineering. *Biomaterials*, 229, 119584.
- [9] Walsh, D. P., Raftery, R. M., Chen G., Heise A., O'Brien F. J., & Cryan S. (2019). Rapid healing of a critical-sized bone defect using a collagen-hydroxyapatite scaffold to facilitate low dose, combinatorial growth factor delivery. *J Tissue Eng Regen Med*, 2019, 13, 1843-1853.
- [10] Denning, D., Kilpatrick J. I., Fukada, E., Zhang, N., Habelitz, S., Fertala, A., Gilchrist, M. D., Zhang, Y., Tofail S. A. M., & Rodriguez, B. J. (2017). Piezoelectric Tensor of Collagen Fibrils Determined at the Nanoscale. *ACS Biomater. Sci. Eng.* 2017, 3, 929-935.

- [11] Liu, Z. H., Pan, C. T., Lin, L. W., & Lai, H. W. (2013). Piezoelectric properties of PVDF/MWCNT nanofiber using near-field electrospinning. *Sensors and Actuators A: Physical*, 193, 13-24.

- [12] Y. Cho, S. Choi, S. Lee, K. Kim and Y. Cho, "Assessments of polycaprolactone/hydroxyapatite composite scaffold with enhanced biomimetic mineralization by exposure to hydroxyapatite via a 3D-printing system and alkaline erosion", *European Polymer Journal*, vol. 113, pp. 340-348, 2019. doi: 10.1016/j.eurpolymj.2019.02.006.