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Nanofibers in Tissue Engineering &Oral Implantology- A Review

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Abstract
Osseointegration in titanium implants is determined by surface topography. Modification of implant surface could be physiochemical, morphological or biochemical. The artificial biodegradable nanofibers produced by electrospinning process mimics extra cellular matrix.This 3D scaffold enhances neo tissue- genesis due to its high surface area, porosity and biodegradability . They are capa-ble of forming networks of highly porous mesh with remarkable interconnectivity between their pores,making them an attractive choice for a host of advanced applications. In fact, the significant impact of nanofiber technology can be traced from the wide range of fundamental materials that can be used forthe synthesis of nanofibers. These include natural polymers, synthetic polymers, carbon-based materials,semiconducting materials, and composite materials. However, to move beyond the current state of nanofibersyntheses and applications towards realization in commercial and industrial settings, several challenges need to be addressed and overcome.This Review explores the applications of electrospunnanofibers in tissue engineering and in oral implantology and the future research directions.

Key Words *– tissue engineering, nanofibers, implant dentistry, electrospinning; bone regeneration; electrospunnanofibers*

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I. Introduction

For over four decades, commercially pure titanium (cpTi) and titanium (Ti) alloys have been used for implant therapy due to their remarkable mechanical properties in loadbearing applications, low density, high corrosion resistance, and biocompatibility.[1] Of note, the basis for using Ti in implant dentistry is predicated on its ability to achieve a direct structural and functional interface with living bone (i.e., osseointegration), which has allowed for the successful restoration of masticatory function in partially and completely edentulous patients. Regrettably, despite accumulating evidence regarding the positive role played by implant surface modification both texture/microstructure and chemistry on bone integration, the risk of infection (peri-implantitis), and thus early implant loss,8,9 still embodies a major clinical concern.

Significant advances in nanotechnology have helped to pave the way toward the development of antimicrobial coatings that could be used to avoid implant infection. Meanwhile, recent research highlighted the prospective anabolic effects associated with tetracycline-derivatives (e.g., doxycycline and minocycline) as their use seemed to enhance cell proliferation.

While tissue-engineered bone grafts have been investigated for years, challenges still lie in achieving *in vivo* mechanical/ biological properties and vascularization for the treatment of patients who suffer from degeneration or diseases such as periodontitis, trauma, oral cancer, and anatomical abnormality in nature. Electrospunnanofibers may be one of the ideal solutions due to their ECM similarity, since they provide control over nanopores similar to the small blood vessel for the cell survival. Electrospunnanofibers have been studied in a variety of the *in vitro* and *in vivo* tests, such as mesenchymal stem cell- (MSC-) seeded implantation into a rat calvarial defect model.

NANOFIBER IN TISSUE ENGINEERING

As an interdisciplinary field combining various Biological and engineering expertise, tissue engineering and regenerativemedicine seek to restore or regenerate the normal tissue andorgan functions using the three fundamental entities of cells,biomolecules, and biomaterials.[1] As one of the most activelyresearched biomaterials, nanofiber-based scaffold emerges asa versatile alternative for tissue engineering and regenerativemedicine applications.[2,3] With their extremely high surface-to-volume ratio and porosity, nanofibers offer a high loading capacityfor biological substances and active species. Furthermore, withtheir interconnected network of micropores mimicking the nativein vivo topographic features of extracellular matrix (ECM), nanofi-brous scaffolds present a favorable avenue for cellular growth,proliferation, and differentiation.

For the particular application oftissue engineering, biodegradable and biocompatible natural orsynthetic polymers are typically used as the nanofiber materials. The specific selection of materials depends very much on thetypes and properties of the tissues to be regenerated as well as theduration of regeneration. An increasing number of studies on theapplications of nanofibrous scaffolds for tissue engineering havebeen reported lately. Some examples are highlighted here.

First, self-assembled chitin nanofibers were synthesized forthe fabrication of biodegradable and flexible substrates micropat-terned through replica molding for engineering cell sheets [4]. Onthe substrates, the seeded fibroblast cells attached and alignedalong the primary axis of the micropatterned features, lead-ing to the formation of ultrathin and free-standing ordered cellsheets which were flexible and could be easily controlled forthe construction of complex tissue structures. Second, alignedgelatinnanofibers-multiwalled CNTs composites were synthe-sized via electrospinning as the scaffolds for the growth ofmyoblast, specifically, for an improvement in the formation ofalignedmyotubes with enhanced contractibility . The activa-tion of mechanotransduction-related genes was upregulatedandthemyotube maturations and contractions were improved throughthe presence of the hybrid scaffolds. Third, electrospunPLGAnanofibers were functionalized with adhesive peptides for car-diac tissue engineering application, specifically for improving theadhesion and contraction of cardiomyoctes[4]. Fourth, biodegrad-able electrospun PCL nanofiber-based scaffolds were coated withplatelet-rich plasma (PRP-PCL nanofibers) to enhance the adhe-sion and proliferation of mesenchymal stem cells (MSCs) .Fifth, multifunctional osteoinductive hybrid peptide nanofiberswere synthesized based on the self-assembly of three bioac-tive peptide molecules and then utilized as an implant coatingto promote bone-like mineralization on a medical grade titanium substrate surface . The nanofibers were functionalizedwithosteoinductive collagen I-derived Asp-Gly-Glu-Alapeptidesequence to increase the adhesion, proliferation, and osteogenicdifferentiation of MSCs into mature osteoblast. Sixth, compositechitosan/silk fibroin nanofibrous membrane scaffolds were syn-thesized based on electrospinning for bone tissue engineering, inparticular, for enhancing the proliferation and osteogenicdifferen-tiation of human MSCs . Apart from that of MSCs, nanofibrousscaffolds are also used for supporting the differentiation of neuralstem cells (NSCs). For example, collagen nanofibrous scaffolds werepreprepared for facilitating the presynaptic maturation of NSC-derivedneurons towards the formation of neural network .More recently, a unique hybrid polycaprolactone-grapheneoxide (PCL-GO) nanofibrous scaffold has been demonstrated toprovide instructive physical cues in guiding the specific differen-tiation of NSCs into mature oligodendrocytes in the absence ofchemical inducers (Fig. 1a) . In the study, biocompatible andbiodegradable polymeric PCL nanofibers were synthesized throughelectrospinning, followed by oxygen plasma treatment. GO, theoxygenated derivative of graphene, was then uniformlycoated on the hydrophilic surface of PCL nanofibers (Fig. 1b).NSCs cultured on the GO-coated PCL nanofibers exhibited exten-sive branching characteristic of oligodendrocytes (Fig. 1c).[4,5] Furthergene expression investigations revealed that cells grown on PCL-GO scaffolds exhibited significant increase in their MBP expression(i.e., mature oligodendrocyte marker) and slight increase in theTuJ1 expression (i.e., neuron marker) while their GFAP expres-sion (i.e., astrocyte marker) decreased simultaneously (Fig. 1d). Byincreasing the concentration of GO, the MBP expression increasedproportionately. This highlights the crucial role of GO in modu-latingoligodendrogenesis as well as the synergistic effect broughtabout by the hybrid PCL-GO nanofibrous composites in promotingthe preferential NSC differentiation towards the oligodendrocytelineage.

For bone regeneration, Kim's group has shown various electrospunnanofibrous scaffolds made of synthetic and natural polymers with or without mineral deposition such as gelatin-PCL , silk-fibroin-PCL , PLA , gelatin- apatite-poly(lactide-co-caprolactone) , mesoporous bioactive glass-incorporated PCL-gelatin, mesoporous silica-shelled PCL , and magnetic nanoparticle-incorporated PCL nanofibrous scaffolds . In addition, a number of polymeric nanofibers have been revealed and used for a cellular platformfor bone, but they lack bioactivity and other biofunctionalities to accelerate bone tissue regeneration. For this, artificial mineralization after fabrication or loading additives (i.e., bioactive nanoparticles and growth factors)

to scaffolds during electrospinning process was introduced and resulted in the induction of osteogenesis by accelerating natural mineralization or vascularization [6,7].

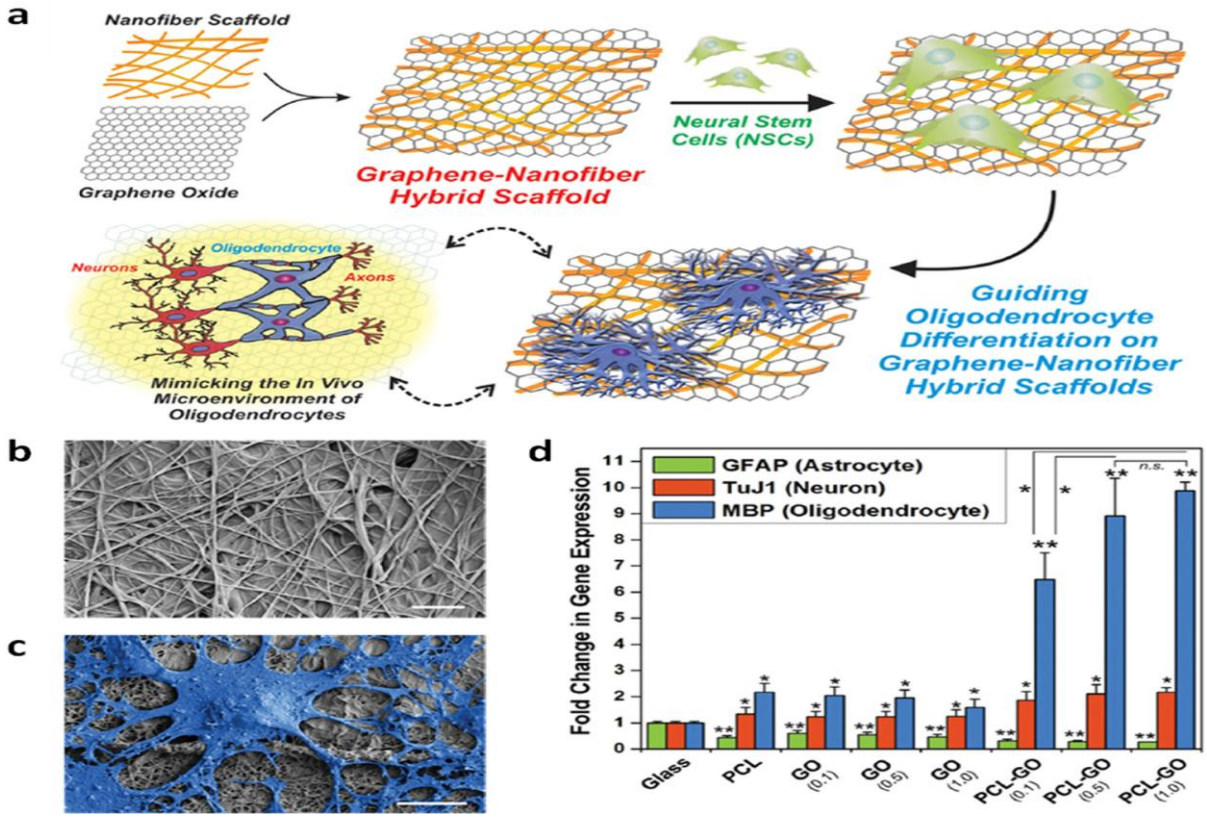

FIG 1 for tissue engineering and regenerative medicine applications. (a) Schematic illustration demonstrating the synthesis and application of the hybrid PCL-GO nanofibrous scaffold in guiding and enhancing the specific differentiation of NSCs into mature oligodendrocyte lineage. (b) FESEM image showing the GO-coated PCLnanofibers using GO solution with a concentration of 1 mg/mL. Scale bar represents 2 _m. (c) FESEM image showing the differentiated NSCs seeded on the hybrid PCL-GOnanofibrous scaffold. Scale bar represents 10 _m. (d) The fold change in the gene expression of the different biomarkers indicative of astrocytes (GFAP), neurons (TuJ1), andoligodendrocytes (MBP), derived from the NSCs cultured on various substrates. The hybrid PCL-GO nanofibrous scaffold demonstrated the highest MBP expression. The *, **,and n.srepresent $p < 0.05$, $p < 0.01$, and no significance, respectively, evaluated based on the Student's unpaired t-test, as compared to the PLL-coated glass control or betweenvarious substrates. [6]

These nanofibrous scaffolds would be employed as a carrier for bone-associated growth factors due to their 3D networked pores to facilitate control over drug release . Recently, electrospunnanofibrous scaffolds were designed to hold a capacity by loading and releasing dual growth factors for the target of bone regeneration. For example, a core-shell structure of a biopolymer fiber made of polyethylene oxide/PCL was shown to facilitate loading and control releasing properties of these growth factors .To increase cell attachment, biofunnctional materials have been used for electrospinning. Silk nanofibers having the Arg-Gly-Asp (RGD) sequence which act as receptors for cell adhesion were shown to accelerate MSC attachment, proliferation, and differentiation into osteoblastic lineage.

Guided tissue Regeneration for Periodontium

One of main advantages of electrospinning is its ability to produce fibers of different orientations and size for fibrous scaffolds for tissue regeneration . Research indicates that these fibers areeffective as tissue regenerative scaffolds because of their ability to mimic the fibrous extra-cellular matrix (ECM) of the human tissues such as bone and cartilage . Indeed, it has been observed thata higher degree of fiber-orientation makes it possible to accelerate proliferation of fibroblasts[4,8]. This has been attributed to an increased surface area and porosity of electrospunscaffolds . Furthermore,changing the fiber orientation also makes it possible to "control" the direction of cellular proliferation as it has been that cells tend to proliferate in the direction of the fiber orientation Many biodegradable materials have been electrospun and revealed the potential to function as GTR scaffolds . Electrospun collagen nanofibers have the potential for GTR scaffolds applications . Additionally, collagen fibers have the potential to allow differentiationof human bone marrow-derived mesenchymal stem cells (MSCs) . However, to date, no studies have attempted to ascertain the mechanical properties of electrospun

collagen fibers. Research hasalso been conducted to produce scaffolds composed of collagen blended with PCL, PEO, PLGA and PLLA . One of the major disadvantages of collagen is that, due to its animal origins, there areethical issues and concerns of cross-infection. Hence, the use of collagen scaffolds could be limited in quite a few demographics.

During the last few years, the idea of functionally graded membrane (FGM) has emerged.[9]

This principle aims to produce a multilayered guided tissue regenerative membrane in which each layer has a specific function and physical properties, very much akin to the natural human tissues .

These layers can contain drugs and various growth factors which be released into the surrounding environment to enhance the regeneration of multiple tissues at the same time . It has beenspeculated that electrospunfibers can form part of these FGMs . Although electrospinning has added exciting new prospects to the field of guided tissue and bone regeneration, much more needsto be explored to validate the use of electrospun scaffolds in the clinical settings. For instance, more research is required to explore the mechanical properties of these scaffolds. More importantly, anadequate number of randomized clinical trials are required to prove their clinical efficacy.[8,9,10]

NANOFIBER IN ORAL IMPLANTOLGY

Dental implants have emerged as options for dental prostheses;however, the presence of biofilm can cause periimplantitis andlead to dental implant loss [11]. Scientists have been studyingsome strategies for creating implants that have an osteointegrative surface while reducing biofilm formation and establishment. PCL/tetracycline nanofibers (5, 10 and 25% wt) were evaluatedfor their antimicrobial ability against periimplantitisrelated microorganisms such as P. gingivalis, F. nucleatum,P. intermedia and A. actinomycetemcomitans. Nanofibers incorporated with 25% wt tetracycline were responsible for inhibiting100% of the biofilm of these bacteria . These nanomaterials may emerge as new implant surface treatments in the futureIn recent years, electrospinning has been deemed a facile approach tosynthesize antibiotic-containing polymer nanofibers withsignificant antimicrobial properties and ability to preventbacterial infection. Worth mentioning, electrospinninghas demonstrated to be a potential method to modifythe surface of titanium implants with nanofibers as a coatingmaterial, contributing to potentially minimize earlyimplant loss, especially in those patients who are at highrisk of periodontal disease.,[10,11,12].

It has been known that upon implantation,a competition exists between implant integration andbacterial adhesion to the biomaterial surface. Notably, a6 h postimplantation period has been deemed crucial to thelong-term success of an implantable device. Collectively, the microbiological data (i.e., TCH-incorporated mats and TCHincorporated fibers-modified Ti disks) demonstrated significantantimicrobial properties against periimplantitis-relatedpathogens.

Marco C. Bottino,et al investigated the antimicrobial and osteogenicproperties of titanium (Ti) disks superficially modifiedwith tetracycline (TCH)-incorporated polymer nanofibers cell viability data revealed that the TCH amounts released by the electrospun mats were not cytotoxic.[3,5,12]

The experiments were carried out in two phases. The first phasedealt with the synthesis and characterization (i.e., morphology,mechanical strength, drug release, antimicrobial activity,

andcytocompatibility) of TCH-incorporated fibers. The secondphase was dedicated to evaluating both the antimicrobialand murine-derived osteoprecursor cell (MC3T3-E1) responseof Ti-modified with TCH-incorporated fibers. TCH wassuccessfully incorporated into the submicron-sized and cytocompatiblefibers. All TCH-incorporated mats presented significantantimicrobial activity against periodontal pathogens.[13]

The antimicrobial potential of the TCH-incorporated fibersmodifiedTi was influenced by both the TCH concentrationand bacteria tested. At days 5 and 7, a significant increase in

MC3T3-E1 cell number was observed for TCH-incorporatednanofibers-modified Ti disks when compared to that of TCHfreenanofibers-modified Ti-disks and bare Ti. A significant increase in alkaline phosphatase (ALP) levels on the Ti disksmodified with TCH-incorporated nanofiber on days 7 and 14was seen, suggesting that the proposed surface promotesearly osteogenic differentiation. Collectively, the data suggestthat TCH-incorporated nanofibers could function as an antimicrobialsurface modifier and osteogenic inducer for Ti dental implants.

Adequate migration and differentiation of mesenchymal stem cells is essential for regeneration of large bone defects. To achieve this, modern graft materials are becoming increasingly important. Among them, electrospunnanofiber scaffolds are a promising approach, because of their high physical porosity and potential to mimic the extracellular matrix(ECM)' Markus D. Schofer et al investigated the the impact of electrospun PLLA nanofiber scaffolds on bone formation in vivo, using a critical size rat calvarial defect model. In addition they analyzed whether directincorporation of bone morphogenetic protein 2 (BMP-2) into nanofibers could enhance the osteoinductivity of the scaffolds.

Two critical size calvarial defects (5 mm) were created in the parietal bones of adult male Sprague-Dawley rats. Defects wereeither (1) left unfilled, or treated with (2) bovine spongiosa, (3) PLLA scaffolds alone or (4) PLLA/BMP-2 scaffolds. Cranial CTscans

were taken at fixed intervals in vivo. Specimens obtained after euthanasia were processed for histology, histomorphometry and immunostaining (Osteocalcin, BMP-2 and Smad5).[4,5,14]

PLLA scaffolds were well colonized with cells after implantation, but only showed marginal ossification. PLLA/BMP-2 scaffolds showed much better bone regeneration and several ossification foci were observed throughout the defect. PLLA/ BMP-2 scaffolds also stimulated significantly faster bone regeneration during the first eight weeks compared to bovine spongiosa. However, no significant differences between these two scaffolds could be observed after twelve weeks.

Expression of osteogenic marker proteins in PLLA/BMP-2 scaffolds continuously increased throughout the observation period. After twelve weeks osteocalcin, BMP-2 and Smad5 were all significantly higher in the PLLA/BMP-2 group than in all other groups.[15,16,17]

They concluded that PLLA nanofiber scaffolds were shown to facilitate cell immigration and thus to achieve high cell densities. However theylacked adequate osteogenic stimuli to allow further differentiationof those cells. The incorporation of rhBMP-2 into PLLAnanofibers could overcome this problem. Hence PLLA/BMP-2implants were able to close critical size calvarial defects within 8weeks. Increased expression of osteocalcin, BMP-2 and Smad5suggests a subsequent activation of the osteoblast lineage.Therefore PLLA/BMP-2 nanofiber scaffolds combine a suitablematrix for cell migration with an osteoinductivestimulus.[18,19,20]

Electrospunfibers as implant interface layer

Electrospunnanofibers are known to facilitate cell adhesion and proliferation in numerous in vitro tests. In vivo studies has also shown low inflammatory reactions. Due to the varied demands of implantables, it is not possible to use electrospunnanofibers in all situations. However, the advantages of electrospunfibers may be employed to facilitate integration between implants and surrounding host tissues. They may also be used to reduce infection through incorporation of drugs and to reduce immune response on the implant

II. Conclusion &Future research directions

Academic studies and research on one-dimensional nanofibersare moving ahead at an incredibly fast pace. Novel synthesis tech-niques and applications of nanofibers are being reported in theliterature at an ever increasing rate and there is no sign of slow-ing down. However, to move beyond the current state of nanofibersyntheses and applications towards realization in commercial andindustrial settings, several challenges need to be addressed andovercome. None of these challenges are trivial, but they are notinsurmountable.

Nanofibrous scaffolds serve as one of the mostexciting alternatives for facilitating the regeneration of many typesof cells and tissues. Although the relationships between a widerange of nanofibrous scaffolds and cells have been investigated, themajority of these studies are still limited to qualitative proof-of-concept investigations of the cytocompatiblity of the nanofibrousscaffolds in terms of cellular adhesion, proliferation, and differ-entiation. Consequently, more attentions should be focused onthe quantitative analyses of the changes in cellular functions asinfluenced by the topographical cues provided by the nanofibrousscaffolds. At the same time, we note that most of the prelimi-nary studies were still conducted in vitro and nanofiber technologyhas yet to make a real impact in in vivo applications. Encouragingresults have been demonstrated in numerous in vitro assays andin a small number of in vivo studies, particularly on animal mod-els, with different categories and degrees of tissue injuries. Clearly,more extensive in vivo studies, possibly on human, and clinicaltrials are needed to evaluate the real impacts and significance of nanofiber technology in healthcare and biomedical engineering.

For the reason, the clinical practice of nanofibrous scaffolds is still scarce. In addition, since dental tissue degeneration may come frombiological disorders, further studies of biological interplaybetween electrospunnanofiber and compromised dental tissuederived cells are essential. These studies will be expectedto help to understand the biological effect of nanofibers.Conclusively, further elaborated techniques to customize

nanofiber scaffolds are imperative, and clinical defects mustbe categorized into several groups for their customization.

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