ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

Research progress of electrospinning bionic periosteum in bone tissue engineering

Suiyan Wei[1], Yijing Cao[1], Guoqiang Xu[1,2,*]

[1]*Department of Prosthodontics, the First Affiliated Hospital of Xinjiang Medical University, School/Hospital of Stomatology, Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region, 830054, China*
[2]*Stomatological Research Institute of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region, 830054, China*
[*]*Corresponding author: 50167745@qq.com*

Abstract: *Periosteum is a vascularized connective tissue capsule covering the surface of bone tissue, which plays a decisive role in the process of bone reconstruction after bone defect. With the rapid development of the field of tissue engineering periosteum, its research direction is to synthesize bionic periosteum which can guarantee or accelerate the repair of bone defects. Artificial periosteum material can be similar to natural periosteum in structure and function and has good therapeutic potential. Electrospinning is an effective method to prepare biodegradable fiber membrane with porous microstructure, and it has a broad application prospect. The ideal bionic periosteum should have biocompatibility and bioactivity, appropriate surface chemical composition, good mechanical properties, and should simulate the natural extracellular matrix (ECM) of bone. Selecting the most suitable material to make bionic periosteum is an important step in the construction of bone tissue engineering. In this paper, the important role of tissue engineering periosteum is reviewed, and the electrospinning technology, including its preparation methods and the latest research progress of electrospinning polymer materials are introduced. Finally, the development prospects and challenges of tissue engineering periosteum based on electrospun nanofibers were summarized.*

Keywords: *bone defect, periosteum, tissue engineering, biomimetic periosteum, electrospinning, nanofibers*

1. Introduction

Critical size bone defects caused by trauma, tumors and congenital diseases need to be repaired by clinical surgery. Due to the lack of a unified treatment plan, the treatment of bone defects is still a challenge for clinicians[1]. Previous studies have focused on optimizing bone implant materials [2], structural design [3], and drug delivery [4] to promote bone repair. The importance of periosteum in phased bone repair was ignored.[5]

Periosteum is the connective tissue capsule that covers the surface of bone. It consists of an inner layer and an outer layer, which contains a variety of osteogenic potential cells and rich capillaries. This complex and multifunctional structure provides a niche for pluripotent cells and molecular factors that regulate cell behavior, allowing the periosteum to serve as a repository. In the stage of fracture healing, the bone progenitor cells in the periosteum differentiate into cells with osteogenic potential, which significantly promotes the recovery of fracture. All components of periosteum are important factors in bone development and regeneration. Periosteum has advanced and outstanding material properties, and its mechanical strength, chemical properties and biological state determine the changes of its material properties. However, autologous periosteal transplantation is limited by limited sources and the health status of patients, which is easy to cause deep tissue infection and chronic pain at the collection site. Allogeneic periosteal transplantation also has some shortcomings, such as immune rejection, easy transmission of pathogens and so on. In order to solve these problems, the tissue engineering method based on periosteal characteristics, efficient artificial periosteum construction technology arises at the historic moment[6,7].At present, the field of periosteal tissue engineering is developing rapidly, and its research direction is to synthesize biomimetic periosteum which can guarantee or accelerate the repair of bone defects. Artificial periosteum material can be similar to natural periosteum in structure and function and has good therapeutic potential. Periosteal tissue regeneration and bone regeneration

ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

induced by bionic periosteum is an ideal method for bone repair. With the development of tissue engineering periosteum, the research of bionic periosteum is becoming more and more mature and reliable. The related research of tissue engineering periosteum not only guides the development of bone tissue engineering, but also provides the possibility for the optimization of bone tissue therapy [8].

At present, various technologies for the development of nanofibers have been reported, such as template synthesis, phase separation, self-assembly, drawing and electrospinning [9]. Among these technologies, electrospinning has more advantages because of its simple manufacture, strong versatility and application potential in different fields. Electrospun nanofibers have received great attention in the fields of tissue engineering, biosensor, filtration, wound dressing, drug delivery and enzyme immobilization.[9] Compared with the traditional technology, the nonwoven nanofiber pad produced by electrospinning can simulate the extracellular matrix (ECM) more closely[[10].

2. Electrospinning technology

Ramakrishna et al. [11] summarized that the process of forming charged liquid jet from polymer solution to prepare nanofibers under the influence of high pressure is called electrospinning process. electrospinning technology has been developed rapidly in the past 20 years because of its advantages such as wide range of applicable materials, easy adjustment, simple operation, low cost and strong variability. Because the nanofiber materials prepared by electrospinning have porous structure, stable physical and chemical properties, adjustable mechanical properties and degradation rate, this kind of materials can be effectively used in biomedical fields such as tissue engineering, drug sustained release, wound dressing and so on. Electrospun nanofibers are a kind of important materials in the research of tissue engineering scaffolds at present, mainly because of their following characteristics: (1) electrospun nanofiber films have good porous structure, high surface volume ratio and space volume. These properties are conducive to the loading and release of bioactive molecules, such as proteins, nano-drugs, nucleic acids and so on. Moreover, the higher surface area is conducive to the contact and adhesion between cells and scaffold materials; (2) the same electrospinning device can be used to produce fibers with diameters of tens of microns or even as small as several nanometers. Nanoscale fibers are similar to the ordered multilayer fiber structure of natural extracellular matrix. As scaffolds, ECM can be well simulated, which is conducive to cell adhesion and proliferation on the surface. (3) single polymer or multiple polymer composites can be used to make nanofiber materials by electrospinning technology. These polymers include a large number of natural polymers, synthetic polymers and their composites to meet the needs of different tissue engineering materials.

3. Electrospinning polymer materials

3.1 Biopolymers

Use has also increased in other industrial and scientific fields, including in medicine, where biopolymers are considered to be promising materials for the production of advanced scaffolds and cell culture substrates. In this regard, the main advantage of biopolymers over synthetic materials is that they are highly bionic and can provide cells with an environment similar to that of natural extracellular matrix (ECM) in morphology and chemical structure. Therefore, biopolymers can stimulate cellular responses similar to those observed in living tissues.

3.1.1 Chitosan

Chitosan is a kind of sugar-based polymer material obtained by deacetylation of chitin. It is probably the most popular example of polysaccharides used in various biomedical applications. Because of its special characteristics, it is also one of the most promising green biomaterials. The extremely hard crystal structure of this polymer leads to its limited solubility in high pH water and a large number of organic solvents. The solubility in aqueous solution was significantly improved when pH was less than 6.5acid. Chitosan is non-toxic, biocompatible, biodegradable and has inherent bacteriostatic and bactericidal properties. It also shows high mechanical strength and high affinity for binding proteins, making it an ideal candidate for biomedical applications. Chitosan has aroused great interest in fiber and biomedical applications because of its high availability, low cost and good biomechanical properties. Therefore, there have been a large number of comprehensive review articles on this subject [12-14].

ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

3.1.2 Alginate

Alginate is a kind of polysaccharides, obtained from the cell wall of brown algae or synthesized by azotobacter and Pseudomonas strains. Alginate has many valuable properties, such as biodegradability, biocompatibility, high hygroscopicity, antibacterial and high ion adsorption. Therefore, it has a high interest in many applications in the biomedical field [15]. Alginate is insoluble in organic solvents, but soluble in water under certain conditions. Because alginate is a polyelectrolyte with rigid intramolecular and intermolecular hydrogen networks, its viscosity is high and its ES tends to be difficult. The aqueous solution can only rotate in a very narrow concentration range, even if there are polymer additives that are easy to rotate [16].

3.1.3 Cellulose

Cellulose has been identified as the first biopolymer to be synthesized into the desired form. The polysaccharide is composed of glucose monomer, is rich in plants, microorganisms and marine flora [17], and exists in a variety of agricultural and industrial wastes (up to 90%). It is a very interesting environmental protection material [18]. Cellulose seems to be one of the limited biopolymers close to clinical application, and long-term studies in rats have revealed its superior performance as an artificial valve [19]. In a recent study, Santos et al [20] synthesized electrospun cellulose acetate fiber and modified it with mahogany extract. The prepared materials are evaluated as wound dressings and can induce antibacterial and anti-inflammatory responses.

3.1.4 Silk fibroin (SF)

Silk fibroin (SF) is a fibrin extracted from the cocoon of silkworm larvae, the most typical of which is extracted from silkworm or Antheraeaassama. SF has a fiber structure and is prone to ES without additives. The feasibility of this process has been confirmed in the literature by ES from formic acid [21-23] or aqueous solution [24]. Zhou et al. [25] and Serodito et al. [26] pointed out in their 2019 paper that no additional stabilization steps are needed. Although Zhou did not provide evidence of long-term fiber stability, Serodito conducted a seven-day in vitro study by implanting human cells from the periodontal ligament (hPDLs) directly into the scaffold. Scanning electron microscope (SEM) images of the experiment showed a maintenance of fiber morphology. Therefore, it is suggested that ultrasound should be used to induce the partial transformation of β sheet before ES, so as to affect the viscosity of the solution and stabilize the formed fiber. SF is a promising material for the preparation of various tissue engineering materials, especially for the treatment of burns or infected wounds.

3.2 Composite polymers

Tt is well known that the application of new biomaterials in hard tissues (such as bones) and soft tissues (such as nerves) poses great challenges to chemists, material scientists and biomedical engineers. The advanced functional scaffolds used in soft and hard tissue engineering should have certain requirements such as biocompatibility, hydrophilicity, porosity and electromechanical properties.

3.2.1 Polyvinylidene fluoride (PVDF)

Electroactive PVDF and its copolymers can generate charge on its surface under mechanical or electrical stimulation, which is very attractive in tissue engineering applications [27,28]. The generated charge and electric dipole stimulate bone remodeling and growth by opening voltage-gated calcium channels [29]. Therefore, the calcium / calmodulin pathway of osteocytes is activated to promote osteogenic differentiation and proliferation [30]. Electrospinning PVDF fiber pad can simulate the structure and electrical response of natural extracellular matrix (ECM), which is considered to have important clinical significance.

3.2.2 Calcium phosphate nanoparticles (CAPS)

However, the lack of inherent bone induction ability limits its application in bone tissue engineering. In order to improve their osteogenic activity, calcium phosphate nanoparticles (CAPS) were introduced into the electrospinning system because of their good osteogenic induction ability. For example, Liu et al [31] combined the prepared CAPS with gelatin methacryloyl (GelMA) by electrospinning to prepare composite hydrogel fibers with the potential to promote osteogenesis. Wang et al. [32] prepared a kind of nanofiber membrane by doping calcium phosphate, which has the ability of bone induction. These studies show that the addition of CAPS can improve the bone induction performance of the polymer, but its ability to promote angiogenesis is weak, which hinders its application in periosteal regeneration.

ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

3.2.3 Polycaprolactone (PCL)

Polycaprolactone (PCL) [33] is a synthetic polyester material approved by the Food and Drug Administration (FDA). It has attracted wide attention because of its good biocompatibility, processability and slow degradation rate for long-term use in vivo[34]. XiangkeZhang et al. [35] successfully prepared a PCL/WH electrospun fiber composite that can promote angiogenesis and osteogenic differentiation by simulating periosteal microenvironment. The incorporation of WH nanoparticles enhanced the bioactivity of PCL/WH membrane. It was observed that PCL/WH membrane could release Mg2+, Ca2+ and PO43-by promoting the formation of apatite in SBF. It can significantly enhance the osteogenic differentiation ability of bone marrow mesenchymal stem cells and the angiogenic ability of endothelial cells. The results of subcutaneous implantation further confirmed that PCL/ WH membrane has good biocompatibility and angiogenic ability in vivo. These results show that PCL/WH membrane has a variety of biological activities and is expected to be used in artificial periosteum.

Piezoelectric materials can generate electric charge to applied stress or small mechanical deformation, so there is no need for external power supply for electrical stimulation. Charge stimulation has a significant effect on cell behavior by affecting the function of ion channels on cell membrane, monitoring membrane potential and regulating intracellular signal transduction pathway. Therefore, the cells can respond to the external electric field both in vitro and in vivo[36]. Conductive polymers such as polypyrrole, Polyaniline, poly (3-ethylenedioxythiophene) and polythiophene have been shown to enhance and guide the growth of axons on their surfaces [37]. However, the use of external power sources for wired electrical stimulation hinders the clinical application of these polymers, thus increasing the risk of infection and inflammation [38].

4. Conclusion

In this paper, the latest research progress of biomimetic nanostructure polymer bone tissue engineering scaffolds is reviewed. But chitosan, alginate, cellulose, deoxyribonucleic acid, silk fibroin, polyvinylidene fluoride (PVDF), polycaprolactone (PCL) polymer and other nanofibers have been used as potential candidates for bone tissue engineering because of their good biocompatibility and easy electrospinning technology. However, the clinical application of biomimetic nanofiber composite scaffolds requires successful interaction among cells, biological signals and biomaterials. However, there are still many unsolved problems and unexplored frontier areas of the role of nanomaterials in bone regeneration.

The new research frontier should be to better simulate the natural process of bone tissue regeneration, such as the coupling between angiogenesis and osteogenesis, which may require the recruitment and differentiation of progenitor cells. Although it is difficult to imitate nature, recent scientific and technological discoveries have shown the potential for bone scaffolds that will promote local and systematic biological functions. The selection of appropriate scaffold materials, their geometric shape, pore size and size distribution, and whether biomolecules can be released at the desired speed will play a vital role in the development of bone scaffolds in the future. In order to better simulate the nanostructures in natural ECM, electrospun membranes have great potential in producing ECM-like scaffolds and effectively implanting bone tissue regeneration in the past decade. Even so, the combination of these materials in the form of nano-scaffolds is still an unexplored field.

References

[1] Pobloth A M, Checa S, Razi H, et al. Mechanobiologically optimized 3D titanium-mesh scaffolds enhance bone regeneration in critical segmental defects in sheep[J]. Sci Transl Med, 2018, 10(423).
[2] Park J, Zobaer T, Sutradhar A. A Two-Scale Multi-Resolution Topologically Optimized Multi-Material Design of 3D Printed Craniofacial Bone Implants [J]. Micromachines (Basel), 2021, 12(2).
[3] Zhang B, Pei X, Zhou C, et al. The biomimetic design and 3D printing of customized mechanical properties porous Ti6Al4V scaffold for load-bearing bone reconstruction [J]. Materials & Design, 2018, 152: 30-39.
[4] B Y Z A, A J H, C S V A B. Biomaterial-assisted local and systemic delivery of bioactive agents for bone repair [J]. Acta Biomaterialia, 2019, 93:152-168.
[5] Ho-Shui-Ling A, Bolander J, Rustom L E, et al. Bone regeneration strategies: Engineered scaffolds,

ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

bioactive molecules and stem cells current stage and future perspectives [J]. Biomaterials, 2018, 180: 143- 162.

[6] Colnot C, Zhang X, Knothe T M. Current insights on the regenerative potential of the periosteum:molecular, cellular, and endogenous engineering approaches[J]. J Orthop Res, 2012, 30(12): 1869-1878.

[7] Rodriguez-Merchan E C. A Review of Recent Developments in the Molecular Mechanisms of Bone Healing [J]. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 2021, 22(2).

[8] Li N, Song J, Zhu G, et al. Periosteum tissue engineering-a review [J]. Biomater Sci, 2016, 4(11): 1554- 1561.

[9] Xue J, Wu T, Dai Y, et al. Electrospinning and Electrospun Nanofibers: Methods, Materials, and Applications [J]. Chem Rev, 2019, 119(8):5298-5415.

[10] Marew T, Birhanu G. Three dimensional printed nanostructure biomaterials for bone tissue engineering [J]. Regen Ther, 2021, 18: 102-111.

[11] Ramakrishna S, Fujihara K, Teo W E, et al. An Introduction to Electrospinning and Nanofibers ||Characterization [J]. 2005,10.1142/5894:192-246.

[12] Kalantari K, Afifi A M, Jahangirian H, et al. Biomedical applications of chitosan electrospun nanofibers as a green polymer - Review[J]. Carbohydr Polym, 2019,2 07: 588-600.

[13] Tao F, Cheng Y, Shi X, et al. Applications of chitin and chitosan nanofibers in bone regenerative engineering [J]. Carbohydr Polym, 2020, 230:115658.

[14] Ranjith R, Balraj S, Ganesh J, et al. Therapeutic agents loaded chitosan-based nanofibrous mats as potential wound dressings: A review[J]. Materials Today Chemistry, 2019, 12:386-395.

[15] Mokhena T C, Mochane M J, Mtibe A, et al. Electrospun Alginate Nanofibers Toward Various Applications: A Review[J]. MATERIALS, 2020,13(4).

[16] Kriegel C, Arecchi A, Kit K, et al. Fabrication, functionalization, and application of electrospun biopolymer nanofibers[J]. Crit Rev Food Sci Nutr, 2008, 48(8):775-797.

[17] Kumar T, Kumar K S, Rajini N, et al. A comprehensive review of electrospun nanofibers: Food and packaging perspective [J]. COMPOSITES PART B-ENGINEERING, 2019,175.

[18] Da Silva B A, Cunha R D, Valerio A, et al. Electrospinning of cellulose using ionic liquids: An overview on processing and applications[J]. EUROPEAN POLYMER JOURNAL, 2021,147.

[19] Bhat A H, Khan I, Usmani M A, et al. Cellulose an ageless renewable green nanomaterial for medical applications: An overview of ionic liquids in extraction, separation and dissolution of cellulose [J]. INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES, 2019, 129: 750- 777.

[20] Tang P, Dai J, Yang X, et al. Research progress of electrospinning nanofibers used in biomedical tissue engineering[J]. Shanxi Chemical Industry, 2018.

[21] Chung S, Ercan B, Roy A K, et al. Addition of Selenium Nanoparticles to Electrospun Silk Scaffold Improves the Mammalian Cell Activity While Reducing Bacterial Growth[J]. Front Physiol, 2016, 7: 297.

[22] Song D W, Kim S H, Kim H H, et al. Multi-biofunction of antimicrobial peptide-immobilized silk fibroin nanofiber membrane: Implications for wound healing[J]. Acta Biomater, 2016, 39:146-155.

[23] Ghalei S, Nourmohammadi J, Solouk A, et al. Enhanced cellular response elicited by addition of amniotic fluid to alginate hydrogel-electrospun silk fibroin fibers for potential wound dressing application[J]. Colloids Surf B Biointerfaces, 2018, 172:82-89.

[24] Singh B N, Panda N N, Pramanik K. A novel electrospinning approach to fabricate high strength aqueous silk fibroin nanofibers[J]. Int J Biol Macromol, 2016, 87: 201-207.

[25] Zhou C J, Li Y, Yao S W, et al. Silkworm-based silk fibers by electrospinning[J]. Results in Physics, 2019, 15: 102646.

[26] Serodio R, Schickert S L, Costa-Pinto A R, et al. Ultrasound sonication prior to electrospinning tailors silk fibroin/PEO membranes for periodontal regeneration[J]. Mater Sci Eng C Mater Biol Appl, 2019, 98: 969-981.

[27] Hoop M, Chen X Z, Ferrari A, et al. Ultrasound-mediated piezoelectric differentiation of neuron-like PC12 cells on PVDF membranes[J]. SCIENTIFIC REPORTS, 2017,7.

[28] Ribeiro C, Sencadas V, Correia D M, et al. Piezoelectric polymers as biomaterials for tissue engineering applications[J]. COLLOIDS AND SURFACES B-BIOINTERFACES, 2015,136:46-55.

[29] Zayzafoon M. Calcium/calmodulin signaling controls osteoblast growth and differentiation[J]. JOURNAL OF CELLULAR BIOCHEMISTRY, 2006, 97(1):56-70.

[30] Jacob J, More N, Kalia K, et al. Piezoelectric smart biomaterials for bone and cartilage tissue engineering [J]. INFLAMMATION AND REGENERATION, 2018, 38.

[31] Rodriguez-Merchan E C. A Review of Recent Developments in the Molecular Mechanisms of Bone Healing [J]. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 2021,22(2).

[32] Wang Z, Liang R, Jiang X, et al. Electrospun PLGA/PCL/OCP nanofiber membranes promote

ISSN 2706-6819 Vol.5, Issue 3: 51-56, DOI: 10.25236/IJFM.2023.050309

osteogenic differentiation of mesenchymal stem cells (MSCs)[J]. Mater Sci Eng C Mater Biol Appl, 2019, 104: 109796.

[33] Meka S, Agarwal V, Chatterjee K. In situ preparation of multicomponent polymer composite nanofibrous scaffolds with enhanced osteogenic and angiogenic activities [J]. MATERIALS SCIENCE AND ENGINEERING C-MATERIALS FOR BIOLOGICAL APPLICATIONS, 2019, 94:565-579.

[34] Yang Z, Yi P, Liu Z, et al. Stem Cell-Laden Hydrogel-Based 3D Bioprinting for Bone and Cartilage Tissue Engineering[J]. Front Bioeng Biotechnol, 2022, 10:865770.

[35] Zhang X, Liu W, Liu J, et al. Poly-epsilon-caprolactone/Whitlockite Electrospun Bionic Membrane with an Osteogenic-Angiogenic Coupling Effect for Periosteal Regeneration[J]. ACS Biomater Sci Eng, 2021, 7(7):3321-3331.

[36] Cortese B, Palama I E, D'Amone S, et al. Influence of electrotaxis on cell behaviour[J]. Integr Biol (Camb), 2014, 6(9):817-830.

[37] Balint R, Cassidy N J, Cartmell S H. Conductive polymers: Towards a smart biomaterial for tissue engineering [J]. ACTA BIOMATERIALIA, 2014, 10(6):2341-2353.

[38] Ateh D D, Navsaria H A, Vadgama P. Polypyrrole-based conducting polymers and interactions with biological tissues [J]. JOURNAL OF THE ROYAL SOCIETY INTERFACE, 2006,3(11):741-752.