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THE PROGRESS OF ELECTROSPINNING MATERIALS IN PERIODONTAL TISSUE REGENERATION

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ABSTRACT

It is a difficult problem for patients and stomatologists to deal with defects of periodontal tissue. The traditional periodontal therapy and the general construction methods of tissue engineering scaffold materials have some limitations. Electrospinning technology is a three-dimensional printing technology that uses electric field force and coulomb force to overcome the surface tension of polymer solutions or melts, and stretch electrospinning materials into micron or nanometer fibers, and is gradually applied in the field of periodontal tissue regeneration. Starting from the perspective of electrospinning materials, this review briefly summarized the recent application of electrospinning technology in periodontal tissue regeneration and prospected its application prospects.

Keywords: Electrospinning, Periodontal tissue engineering, Periodontal regeneration, Electrospun materials

INTRODUCTION

Composed of cementum, periodontal ligament and alveolar bone, periodontal tissue is a complex and delicate functional system that maintains the erection of teeth in the jawbone and can buffer occlusal stress[1]. Periodontal tissue defects caused by systemic systemic diseases or diseases of the oral and maxilla mandibular system are a difficult problem for patients and stomatologists, obviously in patients with chronic periodontitis. Persistent inflammatory stimulation of the periodontal support tissue in patients with periodontitis, often resulting in progressive loss of alveolar bone height, periodontal ligament and cementum, eventually leading to tooth loss[2; 3; 4]. At present, periodontal basic treatment and surgical treatment are often used clinically to control plaque, remove local promoting factors such as dental calculus, and prolong the service life of teeth. However, it is easy to form long combined epithelium and cannot restore periodontal tissue defects, especially the periodontal ligament with a thickness of 0.15-0.38mm.

With the advancement of materials science, cell and molecular biology, as a technique for reconstructing tissue defects and organ damage, tissue engineering has become the main research method for periodontal defects [5]. It consists of three basic elements: seed cells, growth factors and scaffolds. Among them, the traditional methods of constructing scaffolds have many shortcomings, which limit the development of periodontal tissue engineering. Nanofibrous scaffolds based on electrospinning have excellent properties such as high specific surface area[6], bringing new hope for periodontal tissue regeneration. Although the application of electrospinning in the field of

stomatology is gradually increasing, its review on periodontal tissue regeneration is still rare, especially on electrospun materials. Therefore, in this review, we will focus on the types of electrospinning materials, introduce the latest progress of this technology in periodontal regeneration, and prospect its application prospects.

1. Principle and characteristics

Electrospinning technology is an additive manufacturing technology that uses electric field force and Coulomb force to overcome the surface tension of polymer solution or melt, extrudes electrospun material to form a jet stream, and stretches it into micron-scale or nano-scale fibers[7; 8]. By adjusting and improving equipment and printing parameters such as high-voltage supply, syringes, metallic needles, and grounded collector, electrospinning can fabricate complex, delicate, and personalized biomimetic structures, which is favored by researchers[9].

Generally, electrospinning has the following characteristics:①Electrospinning materials should be needed to have a certain viscosity, and can be composite by a variety of materials to achieve printing conditions and complement each other's advantages. The biocompatibility can be improved by modifying the materials. Growth factors, drugs, etc. can also be introduced to add biological functions. ②The diameter of the prepared fibers is similar to that of the natural extracellular matrix, which can simulate the in vivo growth environment of cells to the greatest extent. ③Electrospinning can select the type of material and adjust various printing parameters, and can control the diameter, structure and other properties of electrospun fibers, so that electrospinning has higher porosity and larger specific surface area, which is beneficial for cells. It provides a good environment for adhesion, proliferation, and differentiation, and also facilitates drug release[10].

2. Electrospun materials

In recent years, electrospun materials have become a research hotspot in the field of biomedicine. Polymers are commonly used electrospinning materials, which can be divided into natural polymers and synthetic polymers according to the source route. The characteristics of each material are summarized in Table 1.

2.1. Natural polymers

Natural polymer is an organic polymer with good biocompatibility and biodegradability. The natural polymers used for electrospinning include collagen(COL), chitosan(CS), silk fibroin(SF), gelatin(Gln)etc.

2.1.1. Collagen

COL is the main component of animal connective tissue. It has the advantages of low antigenicity and good biocompatibility, which is beneficial to the adhesion, proliferation and differentiation of cells on the surface of connective tissue.

The rapid degradation rate of COL does not guarantee the stable and predictable space maintenance capacity, which is crucial for periodontal regeneration; the same problem is brought about by the insufficient tensile strength of the membrane.

2.1.2. Chitosan

CS is a white, hard, inelastic, nitrogen-containing hydrophobic polysaccharide that supports the bodies of most marine species [11]. When its degree of deacetylation is greater than 50%, it becomes hydrophilic CS[12]. The structure of CS is similar to the extracellular matrix component glycosaminoglycan, which has good biocompatibility and matching degradation rate in promoting tissue healing. It is also bacteriostatic due to its positive charge after protonation[13]. Thus, it is widely used in the field of tissue engineering.

Table1 Characteristics of some electrospinning materials.

Material	drug	physical properties	Most relevant biological effect	Reference
Gln+CS	AMP@PLGA-MS*	φ=359±174 nm	Good cell adhesion, migration and proliferation properties, bactericidal properties against a variety of bacteria within 1 week	[13]
80%Col+20%CS+tracePCL	—	Diameterφ=282±11nm,thickness: 384±5μm,tensile strength: 6.16±1.43 MPa , porosity:90.4±0.8 % , elongation at break:26.49±1.96%	Better biocompatibility, higher osteogenic activity level than Col group	[14]
Col	—	φ=239±26 nm,thickness: 413±8μm,tensile strength:2.13±0.17 MPa, porosity:92.6±1.2 % , elongation at break:24.03±3.14%	Faster degradation and better osteogenic properties than pure CS group	[14]
90%SF+10%PEO	—	φ=388±37 nm,Viscosity τ =13.1×10-3~21×10-3Pa·s, lose printability ifPEO content exceeding 30%	Excellent mechanical properties	[15]
PCL	Ibuprofen	φ=374±89 nm	Control inflammation and reduce bone resorption	[16]
PCL	5% metronidazole and 5% ciprofloxacin hydrochloride	φ=265±40nm,contact angle:132±1°	Hydrophobicity and thickness can prolong the release of hydrophilic drugs and maintain a certain drug concentration	[17]
PLA/PLGA	nHA	φ=50~500nm, thickness: 2~3μm, contact angle: 106.9°~123.1°	Degradation products can be neutralized by nHA	[18]
PLGA	Fibronectin	contact angle: 130±2°	Biocompatibility; cell attachment rate	[19]
PLA+PVA	BMP	φ=155 ± 61.3 nm,contact angle: 94.5°~127.2°	Nonporous fibers presenting a more effective control	[20]
PCL-PEG-PCL/Zeolite	—	φ=437.9±176.1 nm	Biocompatibility	[21]

***AMP@PLGA-MS: PLGA microspheres loaded with nano-hydroxyapatite nHA and antimicrobial peptide Pac-525.**

CS is adhesive and suitable for electrospinning. However, CS cannot self-gel, and it is easy to aggregate and lose its fiber structure after electrospinning. Therefore, it is necessary to add modifying groups, composite other materials, or add cross-linking solutions such as glutaraldehyde after electrospinning.

Composites of CS tend to have good properties. Studies have shown that compared with electrospun COL films, electrospun COL-CS films have better physicochemical properties, including higher tensile strength and more stable degradation rate[14], and have higher application value.

Silk fibroin

SF is a natural polymer fibrin derived from silk, which has good biocompatibility and hardly causes immune rejection[22]. In addition, its excellent mechanical properties cannot be achieved by other natural polymers [23]. However, electrospinning requires the material to have a certain viscosity, and increasing the concentration of SF in the solution will lead to an increase in the insoluble β-sheet structure and an increase in the brittleness of the produced electrospun membrane[24]. Therefore, it is a common practice to mix SF with other organic or inorganic polymers to form composites. Serodio et al.[15] used polyethylene oxide(PEO)to increase the viscosity of low-concentration SF solutions to achieve good printing performance. However, the content of PEO in electrospun materialswill affect the biocompatibility of the material.

Synthetic polymers

Synthetic polymers are produced industrially from inorganic sources and are divided into absorbable and non-absorbable polymers.

Absorbable polymers are widely used in scientific research and clinical applications due to their ability to reduce the pain of secondary surgical removal, and are predominant in electrospun synthetic polymers. They include polycaprolactone (PCL), polylactic acid (Polylactic acid or poly D, L-lactic acid, PLA/PDLLA), poly lactic-co-glycolic acid (PLGA), polyvinyl alcohol (PVA), polyethylene glycol (PEG), etc. Among them, the most representative synthetic polymer is PCL.

Polycaprolactone

PCL is an FDA-approved biosynthetic absorbable aliphatic polyester. It has good thermal stability and processability, and can be printed into different shapes by melting or dissolving in volatile solvents [25; 26; 27]. In addition, it is hydrophobic, so it can hinder the entry of the solution medium, which is beneficial to control the drug dissolution rate [28]. However, due to its hydrophobic, PCL is not conducive to cell attachment, proliferation and differentiation[29]. Therefore, it is necessary to modify or carry drugs on its surface to endow it with biological functions. Fareeha et al.[16] constructed PCL electrospun nanofiber membranes and transplanted ibuprofen into a mouse model of periodontitis. The research indicated that the functionalized PCL electrospun fibrous membrane had anti-inflammatory effects while promoting the formation of periodontal epithelial attachment.

PCL has been used for a long time and is relatively mature, so researchers often add PCL to multi-component scaffolds. Wang et al. [30] added gelatin-loaded metalloproteinase inhibitors on the basis of PEG-PCL, and demonstrated the effect of multi-component scaffolds on periodontal wound healing through drug release and animal experiments.

Polylactic acid

PLA is hydrophobic and degrades slowly, which limits their use in GTR/GBR. The degradation rate and hydrophilicity of PLA can be tuned by mixing it with PLGA, which degrades faster[18].

Poly lactic-co-glycolic acid

PLGA is a kind of biodegradable synthetic polymers with low toxicity, high customizability, greater stability, and the unique ability of sustained drug release[31]. However, it may release acidic by-products during the degradation process[13], and induce chemotactic aggregation of macrophages to generate immune responses. Studies have shown that spraying nano-hydroxyapatite on the surface of PLGA electrospun fibers can increase the high specific surface area and wettability, which is conducive to cell migration. In addition, the nanoscale rough surface facilitates bone tissue integration. The calcium ions of nano-hydroxyapatite can neutralize the PLGA degradation products, slow down the pH drop, and reduce or avoid the inflammatory response [18].

The researchers also tried to add fibronectin (FN). FN functionalized electrospinning PLGA scaffold, to enhance the viscoelasticity of the material, improve the ability of cell recognition and adhesion, and be beneficial to the healing of periodontal tissue wounds[19].

Polyvinyl alcohol

Consisting of vinyl acetate and vinyl alcohol repeat units, PVA is a particularly promising biomaterial for designing drug carriers with high hydrophilicity, good mucoadhesion, elasticity, high tensile strength, and moderate water solubility at high temperatures. In addition, it possesses a high mechanical properties as it is used as a structural polymer for load-bearing biomedical applications. Since its hydrophilia, PVA is easy to swell and facilitates drug release. Therefore, PVA is often modified with other materials, such as chitosan, to achieve electrospinning[32]. What's more, compared with the properties of the single component, the composite PVA membrane has the advantages of stability, swelling property, biocompatibility and mechanical strength.

Conclusion and Future Outlook

The important research direction of periodontal tissue engineering is to select scaffolds with excellent performance, good biocompatibility, degradability and gradual release, which not only pay attention to anti-inflammatory and bacteriostatic, but also can recruit and induce stem cells to complete periodontal regeneration. Electrospinning technology can use a class of polymers alone or in combination to manufacture scaffold materials with high specific surface area and controllable microstructure to meet the needs of periodontal tissue engineering. However, electrospun fiber scaffolds are thin and cannot mimic the three-dimensional growth environment of cells in vivo. In the aspect of drug delivery, the drug is easy to be released suddenly and cannot achieve a sustained release effect. It is believed that through the joint efforts of researchers such as stomatology, the above problems can be solved and the application value of electrospinning technology can be increased.

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