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Progress in application of natural scaffold materials in pulp regeneration

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Abstract: *Endodontic and periapical diseases are two of the most common oral diseases and usually cause irreversible damage to the pulp due to severe irritation, such as dental caries, accidental trauma, or iatrogenic causes. The typical dental pulp treatment method is root canal therapy, but the loss of dental pulp tissue changes the function of dental pulp, and may cause a series of complications. Pulp regeneration therapy uses the principle of tissue engineering to replace the diseased pulp tissue with new pulp tissue so as to achieve the purpose of restoring the normal physiological function of the pulp. Scaffolds are one of the important elements of tissue engineering, and a variety of scaffolds have been found to potentially be used in pulp regeneration. Naturally derived scaffold materials have good biocompatibility and rapid degradation rate and are widely used in endodontic tissue engineering.*

Keywords: *Scaffold materials; Dental pulp stem cells; Pulp regeneration*

The pulp is a loose connective tissue that exists in a space (the pulp chamber) surrounded by dentin or hard tissue. The external shape of the pulp tissue almost matches the shape of the external dentin[1]. Once bacterial infection of pulp tissue caused by caries or trauma occurs, it leads to inflammation, tissue necrosis, and ultimately to loss of pulp function[2] . Pulp function cannot rely on itself for effective and complete tissue repair and regeneration. At present, the typical clinical treatment is root canal therapy. However, teeth after root canal therapy are prone to changes in pulp defense and sensory function due to loss of pulp, and even tooth fractures[3] . In recent years, pulp regeneration has become a hot topic in stomatology research. Among them stem cells and scaffolds are the basis for tissue engineering of tooth.

1. Stem cells

Stem cells are cells with unlimited self-renewal capacity that induce differentiation into a variety of functional cells for cell replacement therapy, tissue engineering and other research[4] . The possible sources of stem cells in endodontic regenerative medicine are dental pulp stem cells (DPSCs), human exfoliated deciduous dental stem cells (SHED), apical papilla stem cells (SCAP), periodontal ligament stem cells (PDLSC) and so on. Among them, dental pulp stem cells are the most commonly used. DPSCs can induce differentiation into other tissues under certain conditions, such as lipogenesis, neurogenesis, osteogenesis, chondrogenesis, angiogenesis, and dentinogenesis[5] . Pluripotency, high proliferation rates, and easy availability make dental pulp stem cells an attractive source of mesenchymal stem cells for tissue regeneration[6] .

2. Scaffold

Biological scaffold materials are essential in endodontic tissue engineering. The scaffold is a kind of framework or structural basis, should have good biocompatibility, biodegradability , suitable pore rate , can promote cell adhesion, proliferation and differentiation ability, can load signaling factors and other characteristics[7] , support cell adhesion, regulate its proliferation and differentiation and promote tissue formation.

As one of the four elements of tissue engineering research, scaffold materials profoundly affect the biological behavior of cells and their culture efficiency. Materials science applications have evolved from natural materials, synthetic organic polymers to bioceramic materials and composites[8] . Current

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scaffolds for endodontic regeneration include natural source scaffolds and synthetic scaffolds. Synthetic scaffolds lack the bioactive components contained in natural biological scaffolds, so that cells cannot easily migrate, proliferate and differentiate on scaffolds, but their mechanical properties and processable characteristics compensate for this defect and make them materials that can be used for different biomedical engineering. Compared with synthetic scaffolds, natural scaffolds have the advantages of wide sources, easy availability, and better biocompatibility. Common scaffolds of natural origin are polysaccharides, collagen, gelatin, silk, decellularized extracellular matrix (ECM), fibrin, etc.

3. Scaffold of natural origin

3.1 Polysaccharides

Polysaccharides are polymeric carbohydrate molecules composed of long-chain monosaccharide units, which bind together through glycosidic bonds and form monosaccharides or oligosaccharides after hydrolysis. Structurally, they branch from linear to highly. Alginate, chitosan, and hyaluronic acid are the most commonly used materials for pulp regeneration.

3.2 Alginate

Alginate is derived from brown algae or certain seaweeds and is polymerized from mannuronic and guluronic acids. Alginate is an anionic natural polymer material and cells are difficult to adhere to alginate scaffolds. Alginate saline gel is a gel cross-linked by alginate and Ca^{2+} to form a three-dimensional structure with better hydrophilicity and cell adsorption. The simple alginate saline gel lacks animal cell adhesion receptors and can be modified by a variety of methods to change its performance. Connection of bioactive peptide sequences with alginate improves the biological properties of alginate based scaffolds, enhances their interaction with cells, and promotes cell binding and differentiation, such as modification of RGD peptide , YIGSR peptide, GRGDSP to alginate saline gel scaffolds and enhances cell adhesion and proliferation ability[9]. Alginate is nontoxic, widely sourced, readily available, and has good biocompatibility and biodegradability[10] and is currently used in a variety of biomedical applications, including drugs, antibody and/or growth factor (GF) delivery systems, and cell encapsulation and inoculation[7] . Studies have shown that application of TGF-β1 or HCL acid-treated alginate saline gels to human dental slices cultured in vitro induced reactive dentin formation[11] .

3.3 Chitosan

Chitosan, also known as deacetylchitin, is derived from chitin through a deacetylation process and is a linear polysaccharide that connects extracellular matrix to collagen fibers and provides a microenvironment for cell proliferation and extracellular matrix. In addition, the amino groups on its structure can bind to the cell membrane and provide conditions for cell adhesion. Chitosan dissolves at pH H values below 5.5 and forms gels when pH is above 6 or by interacting with multivalent anions. Maria et al[12] removed rat right upper first molar pulp and filled the root canals with chitosan hydrogel and observed newly formed connective tissue with angiogenesis and dentin along the root canal walls at four weeks. Newly formed connective tissue was characterized immunohistochemically and identified as odontoblast-like cells. Increased cell viability, migration and proliferation were analyzed in vitro. Chitosan acts as a carrier for growth factors and bioactive molecules, which are released to increase the expression of odontoblastic markers, thereby inducing the proliferation and differentiation of dental pulp stem cells into odontoblasts[13] . In vivo experiments showed that DPSC s was inoculated into chitosan complex scaffolds containing bone morphogenetic protein-7, and DSPP expression was found to be up-regulated, promoting the differentiation of DPSC s into odontoblast-like cells[14] .

3.4 Hyaluronic Acid

Hyaluronic acid (HA) is a linear polysaccharide found in ECM in many parts of the mammalian body. It is widely used in biomedicine because of its biocompatibility, biodegradability, and non-immunogenicity and is also essential for cell signaling during morphogenesis, inflammation, and wound repair[15] . In addition to this, HA also is non-immunogenic and non-thrombotic, and has a high water affinity and is involved in inflammatory responses, angiogenesis, and tissue regeneration processes[16] . HA hydrogel enhanced cellular metabolism and induced mineralization of DPSCs, which

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are thought to repair dentin-pulp injury[17] . Meanwhile, Silva[18] et al found an HA hydrogel, enhanced with cellulose nanocrystals and rich in platelet lysate (PL), chemotactic and proangiogenic growth factors released from hydrogels containing PL, which stimulate chemotactic and proangiogenic activity by promoting cell recruitment and cell growth and can be used for endodontic regenerative therapy.

3.5 Collagen

Collagen is the most predominant structural protein in mammals and represents approximately 25% of total protein. The molecular structure of collagen, characterized by a high content of diaminodicarboxylic amino acids and carbohydrates, provides cell adhesion well suited for dentistry. On the one hand, the triple helical structure of collagen provides mechanical support to tissues, and on the other hand bioactive peptides derived from collagen play an important role in controlling cell adhesion, cell migration, and tissue repair. Collagen can undergo morphological changes depending on temperature. 4 ° C is liquid and more easily injected into the root canal; coagulation occurs when the temperature rises to body temperature, providing an attachment scaffold for the growth of cells. D PSC s showed a better proliferative effect in three-dimensional medium created from collagen hydrogels compared to conventional cell culture medium[19] . Zhang et al[20] showed that high expression of odontogenic genes such as D SPP and D MP-1 could be detected in dental pulp cells cultured in collagen scaffolds for 6 weeks, and angiogenesis and pulpotoid tissue formation were observed.

3.6 Gelatin

Gelatin is a mixture of peptides and proteins produced by partial hydrolysis of collagen extracted from the skin, bones and connective tissues of animals. Its chemical composition is very similar to that of collagen. Capable of exhibiting a thermally reversible sol-gel transition, thereby melting at higher temperatures and returning to the gel at lower temperatures. Compared to collagen, gelatin is biocompatible, naturally hydrophilic, biodegradable, and non-immunogenic[21] , providing an environment rich in water and similar to the natural extracellular matrix, promoting cell proliferation and migration[22] . The combination of gelatin hydrogel scaffold and blood clot showed the formation of new cementum-like tissue and connective tissue in the root canal, which could repair immature teeth with apical periodontitis[23] . Methacryloyl-modified gelatin-loaded human DPSCs showed effective adhesion, diffusion, and proliferation, while vascularized pulp tissue was observed[24] .

3.7 Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a concentrate of platelets and contains abundant cytokines and growth factors. Autologous PRP has been widely used in stomatology because it releases growth factors and provides an ideal three-dimensional scaffold structure that facilitates stem cell proliferation and differentiation. Xu et al[25] extracted DPSCs from pulp tissue collected from healthy decayed premolars or third molars of patients aged 13 to 25 years. Whole blood samples collected from healthy volunteers with a mean age of 20 years plus ang minus 15 years were centrifuged twice to obtain PRP, and the cells were inoculated into PRP for culture. The results showed that under certain concentration of PRP, the migration and proliferation ability of cells were significantly increased, and the expression levels of DSPP and DMP-1 were increased, indicating that PRP could promote odontogenic differentiation of DPSCs.

Platelet-rich fibrin (PRF) is similar to PRP except that during preparation PRF does not require the addition of any exogenous additives and retains more fibrinogen[26]. Studies suggest that PRF may promote proliferation and odontogenic differentiation of DPSCs via Notch signaling pathway. Three key proteins in Notch signaling showed an increasing trend with increasing PRF concentration in the P RF -treated group, and higher expression of Ki-67, PCNA and odontogenesis-related genes could be detected. Zhang Jian[27] et al found that PRF increased protein and mRNA levels of osteogenic/odontoblastic marker expression detected by qRT-PCR in DPSCs cultured for 21 days which was thought to promote osteogenic/odontoblastic differentiation of DPSCs. Some scholars[28] used PRF to perform root canal revascularization in four immature teeth with necrotic pulp. None of the teeth showed significant symptoms after 18 months of observation, and radiographs showed healing of periapical lesions, continued root development, and apical closure, further verifying the effect of PRF applied to pulp regeneration.

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3.8 Silk

Silk is a natural protein. Recently, its use in medicine has expanded to scaffolds designed for tissue engineering[7] . Silk is composed of fibroin, which is an enzymatically hydrolyzable material and can be processed into water-insoluble implants, such as injectable hydrogels and porous sponges. Silk fibroin has good anticoagulant activity and ability to promote regeneration, good mechanical strength, elasticity, permeability, water permeability and slow degradation rate. María[29] et al inoculated human DPSCs into silk fibroin scaffolds and 2D media, respectively, and after prolonged culture, DPSCs proliferated enough to cover the entire surface of 3D silk fibroin scaffolds, confirming that silk fibroin scaffolds have good biocompatibility for human DPSCs. Zhang et al[30] implanted tooth fragments inoculated with DPSC s silk fibroin composite scaffolds into nude mice, H&E staining showed significant microvascular structure and mineralized nodules at weeks 4 and 8, and positive expression of DSPP and DMP-1 could be detected, indicating that silk fibroin composite scaffolds could induce D PSC s odontogenic differentiation.

At present, there are few studies on the application of silk fibroin in pulp tissue engineering regeneration, but compared with most natural degradable materials, silk protein shows the advantages of good mechanical properties and strong processability, and whether silk fibroin can be used to promote pulp regeneration using the characteristics of strong processability still needs to be studied in the future.

3.9 Acellular ECM

An ideal scaffold must have good biocompatibility, allow adequate cell penetration and attachment, and provide a suitable environment for cell proliferation/ differentiation[31]. Appropriate decellularized tissues can preserve not only the integrity, biological activity and spatial structure of ECM, but also vascular, lymphatic and neural networks. However, any possible residual cellular components in decellularized scaffolds must be removed, as their presence may lead to immune rejection. Decellularized ECM basically preserves the microenvironment and fibrin, mimics natural tissues chemically and mechanically, provides mechanical support for cell seeding and biological 3D carriers, and is considered a suitable natural scaffold material for endodontic tissue engineering[32] . Dental pulp-derived decellularized ECM, which produces scaffolds that support the proliferation, differentiation, and regulation of mineralization[33, 34] of stem cells, has no apparent cytotoxicity. Animal experiments demonstrated that decellularized ECM containing bone morphogenetic protein 4 (BMP-4) bound to DPSCs, and vascularized pulp histogenesis was observed in nude mice[35]. Porcine pulp is structurally similar to human pulp. After decellularization of porcine dental pulp tissue, pulp like tissue can be formed by subcutaneous implantation in nude mice, suggesting that xenogeneic ECM scaffolds are feasible for pulp regeneration[36]. Decellularized ECM scaffolds constructed in vitro from human dental pulp tissue showed that this scaffold provides a suitable microenvironment for DPSCs to support the formation of pulp-dentin complexes[37] . Hengameh[38] et al demonstrated in vitro that decellularized ECM provided a suitable growth environment for DPSCs, with a proliferation rate that increased over time, higher cell migration, and did not interfere with the formation of pulp-like tissue and revascularization in the root canal.

3.10 Fibrin

Fibrin is one of the blood components, which can be used as its own tissue repair scaffold material in tissue engineering. Because it is derived from autologous, fibrin itself or its degradation products are not toxic or produce inflammatory response. Fibrin is a natural scaffold material derived from animal proteins, which has good mechanical and physicochemical properties and can be used as an effective carrier for cells and signaling molecules, providing an environment for cell adhesion in the form of hydrogels, and regulating the differentiation of cell growth[39-41] . Nisarat et al[42] injected fibrin hydrogel into an endodontically devoid root canal, which affected cell morphology and differentiation function in contact with dentin compared to the empty root canal, and promoted tissue growth into the root canal, with newly formed tissue similar to normal pulp. Zhang et al[43] showed that fibrin loading DPSC derived extracellular vesicles as a scaffold could promote the formation of vessel-like structures by increasing the release of VEGF providing new ideas for pulp regeneration.

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4. Prospects

The goal of pulp regeneration is to promote normal pulp function recovery in inflamed or necrotic teeth, which leads to true regeneration of pulp complexes. This review summarizes that some scholars use natural scaffolds for pulp regeneration, and in vivo and in vitro experiments have demonstrated that natural source scaffolds can increase cell adhesion and migration, increase the proliferation rate of cells, promote odontogenic differentiation of cells, and can be degraded in organisms. The extensive basic research results can provide a valid basis for future clinical applications, provide treatment ideas for the realisation of pulp regeneration and provide new directions for the treatment of endodontic and periapical lesions.

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