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Research progress of pulp regeneration based on tissue engineering

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Abstract: *Pulp regeneration has been a research hotspot in recent years. Functional pulp regeneration can not be achieved without the cooperation of stem cells, growth factors and biological scaffolds. Stem cells, as undifferentiated mesenchymal cells, have the potential of multi-directional differentiation and are often used as seed cells in pulp regeneration, playing a key role. As a kind of fertile soil for supporting cell growth, bio-scaffolds can provide a three-dimensional culture environment for stem cells and promote cell proliferation and differentiation. Growth factors are more as the stimulation of stem cell proliferation and differentiation of protein molecules, playing an important role. In this paper, the application of odontogenic stem cells, scaffolds and growth factors in pulp regeneration was reviewed.*

Keywords: *pulp regeneration; odontogenic stem cells; scaffolds; growth factors*

1. Introduction

Pulpitis is an infectious disease in the root canal. It is a common and frequently occurring disease in the oral cavity. At present, the root canal therapy is the main treatment for pulpitis, but the teeth after treatment are lack of neurovascular nutrition, there are still some postoperative complications, the long-term effect should be discussed. Therefore, with the rapid development of cell biology and tissue engineering technology, it has become a new trend to use biological treatment technology for pulp regeneration [1].

Tissue engineering is a technique that combines stem cells, 3D scaffolds and bioactive molecules to simulate the structure of extracellular matrix and promote tissue repair and regeneration[2]. The ultimate goal of pulp regeneration is to restore the necrotic pulp tissue to normal, form a functional pulp-dentin complex, and better preserve the physiological function of teeth[3]. Currently, tissue-engineering-based pulp regeneration therapies mainly include cell homing methods that recruit patients' own endogenous stem cells and odontogenic stem cell transplantation[4] . Because of its high plasticity, good interaction with scaffolds and growth factors, and easy to obtain, odontogenic mesenchymal stem cell has become a research hotspot in the field of pulp regeneration therapy[5]. Scaffolds and growth factors play an important role in pulp regeneration, which can significantly improve the ability of odontogenic stem cells to proliferate and differentiate. However, the large-scale application of this technique in clinical practice still has limitations.

2. Application of odontogenic stem cells in pulp regeneration

Mesenchymal stem cell is an undifferentiated adult stem cell that exists in the oral cavity. It can not only renew itself and keep its stem character, but also differentiate into cells of different tissue types. It is mainly responsible for the maintenance and repair of its related tissues [6], which can be divided into pulp stem cells, human deciduous teeth pulp stem cells, periodontal ligament stem cells, dental follicle progenitor cells and root tip papilla stem cells according to different sources [7].

2.1 Dental Pulp Stem Cells (DPSCs)

As an important source of dental pulp regeneration, DPSCs can be induced into different cell types, such as odontoblasts, osteoblasts and so on, under different conditions *in vitro* and *in vivo*[8]. In the

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process of odontogenesis, DPSCs differentiation contributes to the formation of the third stage dentin. Dentin formation can be regulated by a variety of molecules and pathways[9], contributing to tissue engineering for pulp regeneration. DPSCs not only have the practical advantages of self-renewal, pluripotency and immunomodulation, but also have the functions of repairing dentin and maintaining the vascular and nerve homeostasis of teeth[10]. DPSCs have been widely used in scientific research since 2000, when scientists such as Gronthos first isolated stem cells from dental pulp[11]. In 2020, Long Ling compared the biological properties and regenerative potential of pulp stem cells in immature premolars of beagle dogs and pulp inflammation-induced pulp stem cells. The study has found that inflammatory-induced dental pulp stem cells have biological properties similar to those of normal dental pulp tissues, and that both can mediate regeneration of dental pulp and dentin[12] . Recently, Nazhvani seeded DPSCs onto different scaffold materials and implanted them into the oral cavity of dogs. After 4 months, the pulp-dentin complex could appear in this model[13] , further validates that DPSCs have good prospects in pulp regeneration.

2.2 Stem cells from human exfoliated deciduous teeth (SHED)

Shed cells were first isolated from human exfoliated deciduous teeth in 2003. And SHED proved to be more immature than DPSCs, exhibiting higher levels of osteocalcin expression and alkaline phosphatase activity [14]. SHEDs has been widely used in clinical treatment and research for its easy acquisition, storage and cultivation, self-renewal and multi-directional differentiation[15]. Yuan[16] injected SHEDs and SMS, an injectable simvastatin-functionalized gelatin-methacrylate gel microspheres (SMS) , into human root-cleaning segments and implanted them under the skin of nude mice. The results showed that SHEDs/SMS could induce vascular-rich dental pulp-like tissue *in vivo*. Wu[17] has used autologous SHED to implant in the dental pulp of adolescent patients, which has been proved to have the function of pulp regeneration. It has been proved that the exosomes can significantly promote pulp tissue regeneration and angiogenesis *in vivo* through *in vitro* experiments .

2.3 Stem cells from the apical papilla (SCAP)

The root tip papilla is the soft tissue located at the root tip during the development of immature roots. SCAP is the stem cells isolated from the root tip papilla. These stem cells can be induced to differentiate into odontoblast-like cells. Therefore, it is considered a potential source of dental regeneration and tissue engineering[18] . The ability of Human umbilical vein endothelial cells (HUVECs) to form microvascular capillaries was studied in Gelatin methacrylate (Gelma) hydrogel when BMSC, DPSC and SCAP were coencapsulated with HUVECs. And it was found that SCAP could be passaged up to 20 generations and still retain stem cell characteristics, but its differentiation ability was lower than that of DPSCs, and all of them could promote angiogenesis [19]. SMEDA confirmed from a molecular biology perspective by analyzing the molecular biological conformations and differences of DPSC and SCAP, both of which seem equally applicable to pulp tissue engineering [20].

2.4 Dental follicle progenitor cells (DFPCs)

DFPCs are a group of stem cells located in the dental follicle of tooth germ, derived from neural crest, and are the direct precursor cells of periodontal tissues[21]. With high multidirectional differentiation potential, they are easy to use and are not ethically restricted [22]. Because of these properties, DFPCs have been reported for the repair of intact morphologically mineralized tissue of calvarial and alveolar bone defects [23]. In the area of pulp regeneration, Hong applied DFSCs conditioned medium (DFSCS-CM) to lipopolysaccharide-induced inflammatory pulp stem cells. He demonstrated DFSCs-CM promotes the regeneration of inflammatory pulp through an immunomodulatory mechanism, and showed the therapeutic potential and the application prospect of DFSCs in the treatment of bio-regenerated pulp [24].

3. Application of scaffolds in pulp regeneration

As an essential factor in tissue engineering, scaffolds can provide three-dimensional growth environment for stem cells, keep the original three-dimensional shape of cells. It facilitates gene expression and signal transduction, can enhance the activity of stem cells and the ability of specific differentiation, improve the formation of blood vessels and nerves [25]. Scaffolds can be mainly divided into natural polymer scaffolds and synthetic scaffolds.

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3.1 Natural polymer scaffold materials

3.1.1 Chitosan

As a linear polysaccharide, chitosan has many similarities with extracellular matrix, and has special tensile properties and plasticity [26]. Carvalho demonstrated that chitosan hydrogel scaffolds are a promising platform for cell-homing tissue engineering [27]. Glires-loaded chitosan scaffolds were used in pulp regeneration model in rodents. *In vitro* and *in vivo* experiments showed that chitosan hydrogel combined with blood clot and photobiotherapy could improve the results of pulp regeneration by cell homing [28]. Because of its good biodegradability, biocompatibility and bacteriostasis, chitosan is often used as a carrier of composite materials. It has been found that the combination of calcium hydroxide and β-glycerophosphate can produce stable porous scaffolds. The composite scaffolds can create a micro-environment, which is beneficial to the proliferation and differentiation of dental pulp stem, alkaline phosphatase activity and mineralized matrix deposition [29]. Multidirectional confirmation of its important role in pulp regeneration.

3.1.2 Hyaluronic acid

Hyaluronic acid is a kind of natural polysaccharide which is composed of n-acetylglucosamine and glucuronic acid. Hyaluronic acid is one of the most widely used natural polysaccharides in biomedicine[30]. Previous studies showed that the binding of hyaluronic acid biomaterials to DPSCs may be a good strategy and successfully generated pulp-like tissues with the ability to repair skull defects in a rat model [31]. For the regeneration of the dentin-pulp complex, the complex anatomy of the root canal system and narrow apical passages limit the supply of new blood vessels and the growth of pulp tissue. But the application of hyaluronic acid stent can be well adapted to this pulp cavity shape, easy to model [32].

3.1.3 Collagen

Gelatin is the main component of extracellular matrix extracted from denatured collagen, which is a component of cell adhesion and has good biodegradability and biocompatibility. Choi found that DPSCs adhered well to 3d-printed GelMA and MTA-GelMA scaffolds. And both groups showed better biocompatibility in cell viability assays, and MTA-GelMA scaffolds promoted the differentiation of odontogenic dental pulp stem cells. Therefore, 3D-printed MTA-GelMA scaffold may be a potential biological scaffold for dentin/pulp tissue regeneration [33]. GelMA microspheres loaded with DPSCs constructed by DLP printing technique have been found to provide a soft three-dimensional environment for cell growth, which is beneficial to maintain the dryness of hdpscs and retain the ability of multi-directional differentiation. And it can be used to construct tissue engineering dental pulp. It is hopeful to be used in clinic as tissue engineering therapy for pulp and periapical lesions in the future[**34**].

3.2 Natural ECM scaffolds

Natural extracellular matrix (ECM) scaffolds is known as acellular scaffolds. It is complex network structures composed of macromolecules secreted by cells into the extracellular matrix and are microenvironments suitable for cell survival [35]. Decellularized odontogenic stem cells retain most of the microstructure of the tooth tissue, and carry some of the bioactive factors associated with pulp regeneration and largely retain their original living environment[36]. One of the pulp regeneration-related ECM contains high concentrations of glycosaminoglycans, proteoglycans, and hyaluronic acid linked together by a fibronectin and Collagen-1 network. They are all important for supporting cell growth[37]. By transplanting SHED-ECMS combined with jaw bone marrow mesenchymal stem cell (mscs) into a tooth root fragment model constructed subcutaneously in nude mice. Yang[38] found that the root canal of the tooth root fragment was filled with an interlaced network of pulp-like tissues. A lot of new blood vessels were formed, the continuous new tubular dentin was formed on the inner wall of root canal, the polar arrangement of high columnar odontoblast-like cells was found on the inner side of dentin. And the cell bodies were deep into the dentin tubules, forming the pulp-dentin complex structure. This in turn illustrates the feasibility of acellular scaffolds in pulp regeneration. ECM scaffold material of porous acellular human amnion was used to culture DPSCs *in vitro* and was found to promote the proliferation and differentiation of DPSCs. ECM loaded cells with 30 mg/mL HAM ECM scaffold material for assessment of pulp regeneration in animals *in vivo*. HAM ECM scaffolds not only do not interfere with the formation of medullary tissue and root canals in revascularization, but also have better physical properties and ability to support HDPSC migration [39]. As researchers gain a better understanding of ECM scaffolds, more and more are being developed for pulp regeneration.

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3.3 Synthetic scaffold material

3.3.1 Polymer

At present, the commonly used polymers include polylactic acid, polyglycolic acid, polycaprolactone and so on. PLA and PGA can be degraded into CO_2 and H_2O *in vivo* and finally excrete, which is non-toxic and biodegradable[40]. It can therefore be applied as a scaffold in pulp regeneration. Polylactic-co-glycolic acid is an organic macromolecule synthesized by polymerization of lactic acid and glycolic acid monomers in different proportions. As a kind of material with good biocompatibility and biodegradability, it has become a widely used tissue engineering scaffold material[41]. Gangolli cultured human DPSCs using a double-layer scaffold constructed from biodegradable biomaterial polylactic acid-glycolic acid (PLGA 75:25). The experimental data showed that the scaffolds significantly promoted the dentin differentiation of DPSCs, which may be a potential scaffold for pulp regeneration[42]. However, due to the poor hydrophilicity and cellular affinity of PLGA, and the acid degradation products of PLGA can cause local inflammatory reaction[43]. PLGA often forms composite scaffolds with bioceramic materials. Compared with bioceramics or single polymers, composite biomaterials can obtain better physical and biomolecular properties[44]. Now it has been applied to bone and cartilage, so the polymer has a great prospect as a scaffold for pulp regeneration.

3.3.2 Bioceramics

Hydroxylapatite (HA) is the most widely used bioceramic material in pulp and hard tissue regeneration because of its good bioactivity and degradability. Hydroxylapatite has the ability to neutralize the acidic products of biomedical polymers degraded *in vivo*[45] . The effect of enamel matrix derivative (EMD) coating on the structure of periodontal ligament was studied. Fibrosis in the connective tissue surrounding the EMD-HA group was characterized by a large number of fibroblasts and well-developed capillaries[46]. This result may suggest that it is also possible to promote angiogenesis in pulp regeneration. This provides a new way for clinical pulp stem cells to promote pulp regeneration.

4. Application of growth factors in pulp regeneration

In biology, the term growth factor refers to proteins that can stimulate cell proliferation, cell differentiation and prevent apoptosis. They are typical signaling molecules used for cell-to-cell communication in organisms[47]. Multiple growth factors are involved in the regulation of odontogenic stem cell proliferation and differentiation, such as bone morphogenetic protein (BMP) , transforming growth factor β (TGF-β) , fibroblast growth factor (FGF) and so on[48]. BMP is a group of secretory proteins with highly conserved structure. Growth factors such as BMP2, BMP7, BMP9 have been proved to be active in promoting odontoblast. Wu used BMP2 protein and Nel-like molecule-1(Nell-1) for pulp capping to establish the model of dental pulp injury in mice. The results showed that the expression of specific proteins for dentin formation was stronger in Nell-1 + BMP2 group, it is suggested that Nell-1 + BMP2 has better reparative effect on pulp injury[49] .

TGF-β has at least four subtypes, including TGF-β1, TGF-β2, TGF-β3 and TGF-B1B2. As extracellular ligands, TGF-β can activate downstream target genes by binding to membrane receptors. Furthermore, they regulate tissue repair and embryonic development, cell growth, differentiation and immune function. Many studies have shown that TGF-β1 can promote the proliferation of dental pulp stem cells, promote osteogenesis, odontogenic differentiation and nerve repair. It plays an important role in the process of dental pulp injury and repair [50].

FGFs are a class of polypeptides that not only play an important role in the repair of cardiac endothelial cells, but also have great potential in the development, repair and regeneration of damaged skeletal tissues [51]. FGFs are often used to rapidly resolve inflammatory responses in tissues, promoting the recruitment, proliferation, and angiogenesis of endogenous stromal cells for bone repair[52]. Among them, fibroblast growth factor 2(FGF2) is expressed in both odontogenic mesenchymal stem cell. It is mainly involved in tooth development, pulp homeostasis and dentin repair[53]. In regenerative medicine, the introduction of these important cytokines has significantly improved the ability of stem cells to proliferate and differentiate.

5. Outlook and summary

To sum up, in the pulp regeneration of odontogenic stem cells, biological scaffolds, growth factors

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complement each other. Between them can be through precise regulation, play the greatest advantage for pulp regeneration provides a huge possibility. However, there are still many difficulties in applying this biotherapy technique to clinical practice. For example, which kind of odontogenic stem cells can differentiate better? How to make the biological scaffolds suitable for odontogenic stem cells proliferation and differentiation? And what kind of growth factors to add? It is the key to the successful clinical application of tissue engineering based pulp regeneration in the future, and is also the most important to understand the molecular mechanism of tooth development.

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