Emerging Strategies for Pulp Regeneration: A Comprehensive Review and Clinical Perspectives

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Abstract: Irreversible process pulpitis has brought great pain to patients, and traditional treatment methods have some limitations. Pulp regeneration therapy aims to restore the function of damaged tooth hard tissue and pulp, and can be divided into young permanent tooth apical tissue regeneration and mature permanent tooth pulp regeneration. Root tip induction and revascularization can be used to induce the closure of apical foramen in young permanent teeth. The former has a wide range of applications, but there are problems such as long treatment cycles and low success rates. Revascularization is an emerging method in recent years that has achieved good clinical results. For mature permanent teeth, the ability of autogenous regeneration is limited, and Stem-cell therapy, utilizing tissue engineering techniques, can promote pulp regeneration, but it is still in the experimental research stage. Different types of scaffolds and growth factors play an important role in pulp regeneration. At present, there is a lack of unified induction and comprehensive clinical and experimental evaluation of methods for pulp regeneration. Therefore, this article reviews the strategies for pulp regeneration and evaluates the advantages and disadvantages of each method, in order to improve the success rate and effectiveness of clinical application.

1. Introduction

Irreversible process pulpitis causes severe pain in patients, making it difficult for them to eat and sleep, significantly impacting their quality of life [1]. Traditional treatment methods for this condition include root canal therapy, apical barrier surgery, and apexification [2-6]. However, root canal therapy can lead to brittleness in the tooth's hard tissue due to the loss of nutritional supply, increasing the risk of tooth splitting [7]. Additionally, root canal therapy has a certain failure rate due to the complexity of the root canal system, making it challenging to completely remove anaerobic bacteria and their toxic products, leading to repeated infections and bone destruction [8-9]. Pulp regeneration therapy, as a cutting-edge method for restoring damaged dental hard tissue and pulp function, has received widespread attention in recent years. However, current treatment methods have some limitations, especially in the lack of unified induction methods and comprehensive evaluation standards, which directly affect the success rate of treatment and the wide range of clinical applications.

In young permanent teeth with incomplete apical closure, performing apical barrier surgery directly can result in a poor crown/root ratio and thin root canal walls, increasing the risk of root fracture [10]. The current traditional method for inducing root tip growth is apexification, where calcium hydroxide and other drugs are used for root tip induction, a procedure to stimulate the continued development of the root apex. However, research has shown that the success rate of apexification is unsatisfactory, and the lengthy diagnosis and treatment process for children often leads to treatment failure due to patients not following up on time [3-4]. Furthermore, the induced calcification barrier is porous and cannot effectively seal the root tip. Current research focuses on maintaining pulp vitality, reversing inflammation, and inducing apical development.

Pulp regeneration, also known as regenerative pulp treatment, aims to form pulp-like tissue in the pulp cavity to promote the repair of damaged tooth hard tissue and functional recovery of the pulp-dentin complex [11-13]. It can be divided into apical tissue regeneration for young permanent teeth and pulp regeneration for mature permanent teeth based on the patient's tooth development stage. Commonly used methods include revascularization and stem cell implantation [3,4,16-20]. As mentioned earlier, apexification can continue tooth root development and reduce or seal the apical foramen, but it requires frequent visits, has long treatment cycles, and is less effective for adult teeth [4,16]. Revascularization surgery can improve the success rate of treatment by promoting vascular regeneration, which is crucial for healing and regenerating dental pulp tissue. Dental pulp revascularization has a high survival rate in theory, and postoperative root development is favourable, including root length extension and pulp wall thickening [17-18]. In addition to revascularization, tissue engineering often utilizes stem cells and scaffolds to regenerate dental pulp. Dental pulp stem cells are the most suitable cell source for dental pulp-dentin regeneration due to their high differentiation potential, and autologous stem cell

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transplantation can avoid immune responses [13]. Bioactive scaffolds, such as natural polymer scaffolds, synthetic polymer and bioceramic scaffolds, and composite scaffolds, provide a favourable microenvironment for dental pulp regeneration. The specific growth factors bound to the scaffold can attract stem cells, induce their differentiation into dental pulp-like tissue, and promote the formation of dental pulp tissue. Developing tissue regeneration scaffolds is challenging as they need to exhibit high biocompatibility, enhance cell proliferation and differentiation, and bind inducible growth factors [19-20].

Ongoing research on dental pulp regeneration explores diverse topics and treatment methods, each with its own merits and drawbacks. Some treatment methods are still in the early stages, and the clinical failure rate is high [7]. Additionally, there is a lack of unified selection criteria and prognosis evaluation. Therefore, this article provides a comprehensive review of different pulp regeneration methods, their advantages, disadvantages, and clinical effects, aiming to facilitate clinical selection and application.

2. Pulp regeneration at different ages

2.1 Apical tissue regeneration of immature permanent teeth

The roots of immature permanent teeth are generally not fully developed, and the apical foramen are not closed. During the treatment process, problems may occur, such as incomplete apical insertion, inability to fill the root cannel properly, insufficient root length, and fragile root. Therefore, if the pulp of young permanent teeth undergoes lesions, it is very important to promote the continued development of periapical tissue and induce apical foramen closure after eliminating inflammation [14]. In the early stage of tooth root development, the Hertwig's epithelial root sheath, dental papilla, and dental sac interact to form a comprehensive functional complex, known as the developing apical complex (DAC). DAC cells have strong proliferative and mineralizing abilities, as well as certain anti-infective abilities. The dental pulp stem cells have been successfully isolated and used for clinical treatment, providing a histological basis for developmental apical tissue regeneration. Current research shows that apical induction and revascularization are the most commonly used methods to induce the continual development of young permanent root tip [14-16]. However, these existing clinical technologies have certain drawbacks, such as longer treatment cycles, requiring more multiple visits from patients, and easier treatment failure due to persistent infections. The limited availability of autologous stem cells and their sensitivity to inflammation are key factors. So, research has found that using exogenous or autologous stem cells in combination with scaffolds and growth factors can achieve good results. Research has shown that platelet-rich plasma (PRP) containing various growth factors can promote the expression of dental angiogenic factors, and enhance the regeneration of vascular tissue of the dental pulp, thereby promoting the continual development of dental roots and restoring dental vitality. Bioactive scaffolds and growth factors can provide an ideal microenvironment for stem cells to promote dental pulp regeneration [19].

2.2. Pulp regeneration of mature permanent teeth

Due to the complete development of mature permanent teeth root tips and the scarcity of stem cells in most dental pulp, once the pulp becomes inflamed, the inflammatory state is difficult to reverse. Therefore, current treatment methods mainly use root canal therapy. However, the hard tissue of teeth after root canal therapy is prone to discoloration, embrittlement, root splitting, and even tooth extraction. Therefore, current researches focus on how to regenerate damaged dental pulp to restore tooth nutrition supply, and reverse inflammation. Due to the lack of apical papilla stem cells in mature permanent teeth, methods such as promoting endogenous stem cell homing or transplanting exogenous stem cells can be used. However, the homing effect of stem cells after stimulated by inflammation in mature permanent teeth is poor, so current researches mostly use exogenous transplantation methods. Externally transplanted stem cells include dental pulp stem cells (DPSC), stem cells from human exfoliated deciduous teeth (SHEDs), stem cells from the apical papilla (SCAPs) and other tissue-derived mesenchymal stem cells. These mesenchymal stem cells originate from neural crest or glial cells and have high proliferation, self-renewal ability, and potential for multi-directional differentiation. They can induce the formation of nerve and vascular and achieve the regeneration of vascularized dental pulp tissue. In addition, stem cells have the ability to form dentin, which is conducive to the formation of the pulpo-dentinal complex. Currently, it is believed that DPSCs are the ideal choice for stem cell transplantation of dental pulp regeneration, as they are non-antigenic, so they do not cause an immune response in vivo. Previous studies have shown that in the root canal implanted with dental pulp stem cells, vascularized dental pulp tissue is generated and dentin like deposits are observed on the canal wall, which can restore sensory function to a certain extent. However, due to the limited survival time of stem cells in mature permanent teeth and the inability to completely remove inflammatory factors, clinical applications are still limited.

3. Means of pulp regeneration

3.1 Traditional apexification

Apexification is a traditional method to promote the continued development of tooth roots, mainly treating young permanent teeth with severe pulpitis or periapical inflammation. The purpose is to use drugs to induce the formation of the root tip and periapical hard tissues, on the basis of eliminating bacterial infections and curing periapical inflammation, in order to continue the development of the tooth root and narrow or close the apical foramen for permanent root canal filling. Apexification can continue the development of tooth roots, mainly relying on the residual living pulp at the root tip, the dental papilla at the root tip, and the Hertwig's epithelial root sheath preserved in the periapical tissue. The multipotent cells in it can differentiate into odontoblast-like cells, promote the deposition of dentin, thicken the root canal wall, extend the root, and close the apical foramen.

In clinical treatment, apexification has formed a relatively complete and standard treatment procedure. Firstly, sufficient root canal preparation and chemical flushing are performed under rubber barrier isolation, followed by drug induction using calcium hydroxide preparations such as Vitapex, and temporary sealing the cavity with glass-ionomer cements. After treatment, it is necessary to follow up every 3-6 months and take X-ray films until the root is extended, the apical foramen is closed or a calcified barrier is formed at the apex, which can be followed by routine root canal therapy. In the treatment, the key drug is calcium hydroxide, which can be used as both a disinfectant and an inducer. Calcium hydroxide has strong alkalinity, which can fully inhibit bacterial proliferation and neutralize acidic bacterial products. It can also induce differentiation of periapical tissue cells, promote cementum formation, and induce residual dental pulp to form bone like dentin, allowing tooth roots to continue to develop.

However, in practical applications, apexification has certain drawbacks. According to reports, the success rate of apical induction plastic surgery is 60% -85% [7], and it cannot fully achieve satisfactory results. In addition, due to the varying time required for root development, which is mostly around 6 months to 2 years, it requires high cooperation from the patient and their family members to undergo a follow-up every 3-6 months. In addition, the therapeutic effect of apical induction shaping surgery is highly dependent on the activity of the Hertwig's epithelial root sheath in the living pulp, dental papilla, and periapical tissue present at the root tip, which results in poor therapeutic efficacy for patients with longer and larger lesions. Moreover, for adult patients who have exceeded the root development time, the treatment effect is also difficult to predict [7]. Therefore, in recent years, several new technologies have emerged to compensate for the shortcomings of apexification.

3.2 New methods

3.2.1 Pulp revascularization

When inflammation occurs in the dental pulp, although the coronal and root pulps are severely affected. However, due to the presence of stem cells in the apical tissue, these stem cells have strong differentiation potential and can form vascular like dental pulp tissue, promote the formation of mineralized tissue in the root canal, and promote the continual development of the root and the closure of the apical foramen [17]. According to this principle, revascularization surgery is applied in clinical practice. At present, the commonly used method in clinical practice is to use 5.3% NaClO irrigation, calcium hydroxide or ciprofloxacin with metronidazole paste for disinfection and sterilization for 3-4 weeks after conventional root canal preparation. Next, a sterile No. 20 K file was used to extend beyond the apical foramen to cause bleeding, filling the apical area with blood, and placing a mineral trioxide aggregate (MTA) above the blood clot. Finally, the cavity was tightly filled. Treatment can be combined with the use of drugs that induce angiogenesis, such as iloprost. The key drug for vascular regeneration surgery is MTA. MTA has strong sealing ability, stability, biocompatibility, and strong antibacterial properties, which can promote the growth of cementum and the formation of new bones. Correctly operated revascularization can achieve significant clinical results, with a success rate of 88%. In the follow-up observation at 1, 3, 6, 12, and 24 months after surgery, all patients showed improvement and healing of periapical inflammation, without clinical symptoms and signs such as percussion and palpation pain, swelling, sinus, and pathological tooth movement . Even, restorative reactions similar to those of normal dental pulp can appear. Most patients can experience significant thickening of the dentin wall, root elongation, and closure of the apical foramen one year after surgery. Compared to apical induction plastic surgery, it greatly shortens the treatment cycle. In addition, the root resistance after revascularization surgery is enhanced, which significantly reduces the risk of tooth fracture compared to apexification.

It should be noted that thorough root canal cleaning and effective microbial control are crucial for the success of revascularization. In clinical practice, NaClO flushing combined with calcium hydroxide or triple antibiotic paste (TAP)—metronidazole, minocycline, and ciprofloxacin—chemical disinfection schemes are mostly used to reduce microbial burden. However, the use of TAP may produce cytotoxicity and may cause dentin discoloration, so it can be combined with host defense peptides (HDP) to exert antibacterial effects and regulate immune responses.

Although revascularization has achieved significant clinical results, it still has certain drawbacks. The requirements for sterile conditions in revascularization surgery are relatively strict. And operating under a microscope greatly increases the technical difficulty. In addition, the main drug for revascularization, MTA, is expensive. Revascularization surgery is limited to the treatment of young permanent teeth and has poor therapeutic effects on teeth after trauma.

3.2.2 Stem cell therapy

Due to the limited number of endogenous stem cells homing in revascularization, there are currently methods that consider obtaining stem cells through exogenous methods. Stem cell therapy or tissue engineering therapy involves implanting stem cells cultured in vitro into the body, utilizing the multi-directional differentiation characteristics of stem cells to repair diseased tissue or reconstruct normal functions of cells and tissues.

In tissue engineering, the three core components of dental pulp regeneration include stem cells, scaffolds, and growth factors (GFs) [19]. Among them, stem cells are particularly crucial. Transplanted stem cells not only directly participate in the regeneration process, but can also regulate the regeneration process by producing building blocks and secreting nutritional factors. Multiple types of stem cells can be isolated from teeth, such as DPSCs, SHEDs, SCAPs, etc. DPSCs are the first stem cells isolated from adult dental pulp with strong proliferation and differentiation abilities, capable of differentiating into odontoblast-like cells and osteoblasts, promoting the generation of dentin and bone. SHEDs can not only differentiate into bone and dentin, but also into other mesenchymal and non-mesenchymal stem cells, such as adipocytes and nerve cells, and their proliferation rate is faster than DPSCs. However, there are still defects in forming a complete dentin pulp complex in the body. SCAPs have higher proliferation and mineralization potential, making them more suitable for tissue regeneration than DPSCs .

An ideal biological scaffold has good biocompatibility, appropriate porosity and conductivity, the ability to bind growth factors, appropriate mechanical properties, and biodegradability. It can provide a three-dimensional growth space for stem cells to exert cellular function and metabolism, promote cell regeneration and multi-directional differentiation potential, and stimulate stem cell proliferation and differentiation into odontoblast-like cells.

Concentrated growth factors (CGFs) packaged in scaffolds can be dissolved and continuously released through fibrin, including transforming growth factors (TGFs)- β1, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), bone morphogenetic protein (BMP), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF), among others [19]. This increases the regulation and induction of stem cells, and upregulates the homing and differentiation of stem cells in both time and space. At present, the commonly used scaffold for dental pulp regeneration together with stem cells is hydrogel scaffold. Hydrogel has great advantages in mimicking extracellular matrix. At present, most types of hydrogel scaffold combined with stem cells can form connective tissue with varying degrees of similarity to dental pulp.

At present, stem cell therapy is mainly limited to experimental research. Widbiller M et al. made progress in a mouse model by flushing the root canal wall with EDTA, filling the root with specific fibrin containing growth factors and plasma rich in growth factors, and placing dental pulp stem cells at the root tip. Then, the construct was implanted into immunocompromised mice and incubated for 4 weeks. Thus, it can be concluded that fibrin derivatives can be used to manufacture scaffolds and induce the formation of dental pulp like tissue. There are also a few clinical cases that have achieved satisfactory results. Eren K et al. implanted platelet-rich fibrin obtained from the patient's blood into the disinfected root canal, and extracted and isolated dental pulp stem cells from the patient's inflamed pulp. After expansion, they were implanted into the blood clot in the root canal, and then tightly filled. After 6 months and three years of follow-up, the patient's dental pulp showed delayed response to cold testing and positive electrical activity test.

Similar to vascular regeneration surgery, the implantation of stem cell composite scaffolds also needs to be carried out under strict sterilization conditions. However, in response to the cytotoxicity of sodium hypochlorite and the drawback of discolouring dentin, the method of adding ethylene diamine tetraacetic acid (EDTA) to the flushing solution can not only increase the vitality of DPSC, but also induce DPSCs attachment and differentiation of osteoblasts/osteoblasts, It can also stimulate the release of angiogenic GFs in the dentin matrix .

In current research, the application of stem cell composite scaffolds has mostly achieved ideal results in vitro experiments, but it is still in the research stage and has not been fully applied in clinical practice [19]. Moreover, if the concentration of growth factors is too high, it may have certain side effects. For example, excessive concentration of rh-BMP2 may lead to side effects such as bone overgrowth, increased cancer risk, toxicity to other parts, and may have an impact on distal organs. In addition, the differentiation of stem cells is multi-directional, making it difficult to induce their directional differentiation(table 1) .

Table 1. Comparison of advantages and disadvantages of common dental pulp regeneration methods.

	Apexification	Revascularization	Stem cells+ Scaffold +GFs
Advantages	Ability to induce formation of apical hard tissue, continue root development, and narrow or close apical foramen	Compared with apexification, significant thickening of the dentin wall in the apical area, periapical lesion recovery, root elongation, apical foramen closure, and restorative response in more patients, resulting in a higher success rate and a lower risk of fracture.	a. Availability of exogenous stem cells in large quantities by laboratory culture, compensating for the low homing volume of endogenous stem cell b. Stem cells that can grow in three dimensions in scaffolds with high self-renewal capacity c. Growth factors that significantly promote stem cells osteogenic and vascular differentiation [19]
Disadvantages	a. High frequency of visits and long treatment cycles b. Lower success rates c. Young permanent teeth only [7]	a. Seriously affected by micro-organisms, must be strictly sterilized b. Antimicrobial drug use that may produce cytotoxicity and may lead to dentin discoloration c. Poor results in teeth with traumatic pulp necrosis d. Young permanent teeth only	a. Mostly in vitro experiments and insufficient clinical application to assess effects yet b. Possibly increasing inflammatory response due to high concentrations of growth factor use c. Uncertainty in targeted differentiation of stem cells [19]

4. Classification of commonly used scaffolds

Biological scaffolds are structures that provide three-dimensional growth space for cells and regulate cell function and metabolism. Biological scaffolds play a crucial role in the process of dental pulp regeneration, as they can attach and release growth factors, create a favourable microenvironment for dental stem cells, and promote their proliferation and differentiation [19]. Due to the low survival rate and degree of proliferation and differentiation of transplanted stem cells alone, the application of scaffolds greatly improves the success rate of dental pulp regeneration. According to the materials of the scaffolds, it can be divided into natural polymer scaffolds, synthetic polymer scaffolds, and bio-ceramic scaffolds. Natural polymer scaffolds, such as alginate, cellulose, collagen, etc., have high biological safety and can be degraded, but their mechanical strength is low. Synthetic polymer scaffolds, such as polylactic acid and self-assembled peptides, have high mechanical strength but have a measure of cytotoxicity and are not easily degraded. Bio-ceramic scaffolds, such as calcium phosphate and bioactive glass, have good bone binding properties, but there are currently few cases of their application in dental pulp regeneration, instead, they are mainly used in maxillofacial bone regeneration. Currently, there are various materials available for dental pulp regeneration scaffolds, with their own advantages and disadvantages.

5. Common growth factors

Growth factor is a signal molecule that can bind to specific cell membrane receptors and regulate cell function, playing an important role in promoting stem cell proliferation and regulating its function. Due to the non-directional differentiation of dental pulp stem cells, it is often necessary to package growth factors in scaffolds to introduce growth factors to provide a regenerative microenvironment, thereby improving the proliferation, directional differentiation, and migration of the stem cells during dental pulp regeneration. Among them, TGF-β1, BMP-2,4,7, bFGF, stromal cell-derived factor (SDF)-1,etc. have the effect of promoting dentin deposition; PDGF, IGF-1,VEGF,bFGF,granulocyte-colony-stimulating factor (G-CSF), SDF-1,etc. have the ability to induce angiogenesis; bFGF, G-CSF, SDF-1, etc. can induce neurogenesis; bFGF and other factors have the effect of promoting multi-directional differentiation of stem cells; TGF- β 1 can participate in the immune response; bFGF, G-CSF and others can resist apoptosis. Their specific functions are shown in Figure 1.

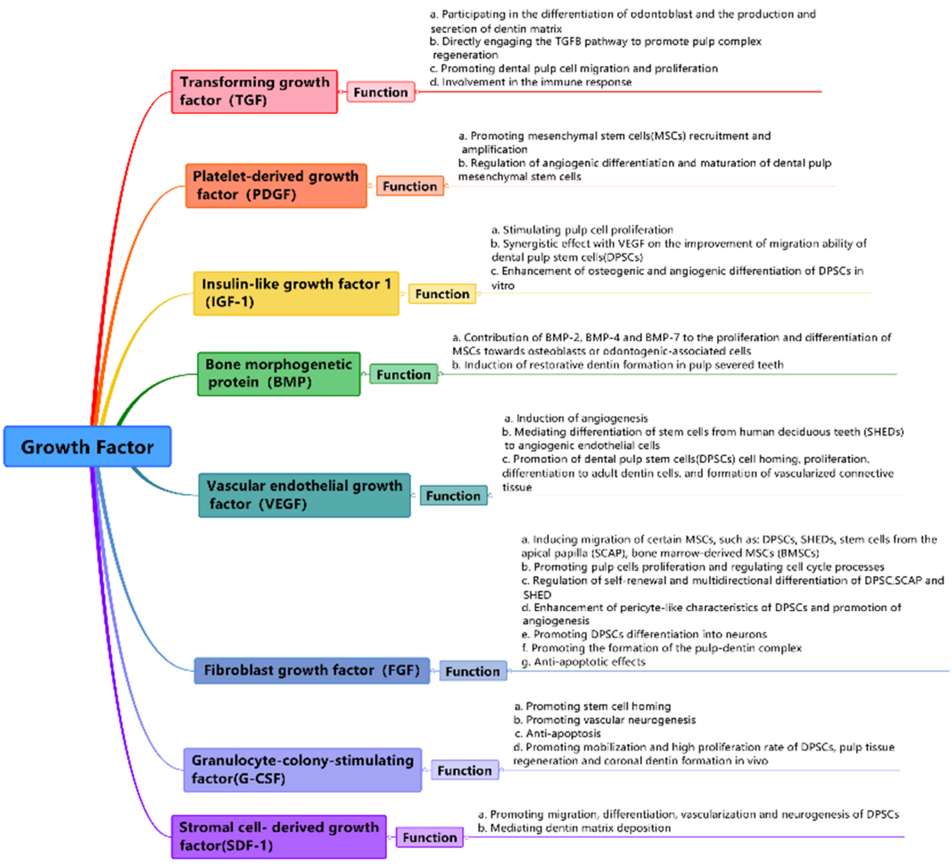

Fig. 1. Common growth factors applied to pulp regeneration and their functions. Various types of growth factors can be used as supplements for pulp regeneration to promote the proliferation and differentiation of stem cells and to enhance the regenerative effects of the tissue. The more commonly used growth factors include TGF-β1, PDGF, IGF-1, BMP, VEGF, FGF, G-CSF, SDF-1, etc.

6. Effect evaluation

Root tip induction and revascularization have been widely used in clinical treatment. In follow-up after 12 to 48 months, the success rate of immature permanent teeth with necrotic and trauma treated with revascularization was 88.3%, and 75.9% of the teeth had closed apical foramen. The average reduction in apical diameter was 1.15mm, the average increase in root length was 1.26mm, and the average thickening of root canal wall was 0.52mm. However, in the report by Mittmann et al., the success rate of revascularization for severely injured teeth (75% of cases are severe avulsion, 19% are dislocation, and 6% are embedded cases) is relatively low, at 44%. And 9.69% of traumatic immature necrotic permanent teeth treated with revascularization showed crown discoloration, which may be due to the use of root canal disinfectant TAP or the effect of bismuth oxide in MTA. C. Caleza Jim é nez et al. compared the X-ray images of 18 necrotic immature permanent teeth at 6 months after apexification and revascularization. After revascularization, root growth increased in terms of root length and dentin thickness, accounting for 12.75% and 34.57%, respectively; After root tip induction, the change in root length was only 0.29%, and the widening of root canal wall was only 7.49%. In the case of the application of revascularization in immature replanted teeth, Ayman M Abulhamael et al. reported that during a follow-up visit of 6 months after revascularization, the patient developed a sinus tract and underwent apical barrier technique using MTA. During follow-up observation, the teeth were intact. Besides, periapical repair and apical closure and calcification were observed at 4 mm of the root tip in the root canal. In cases of periapical abscess treated with revascularization, Wan-Chen Chen et al. reported that during follow-up observations of 6 months and 1 year, the patient did not show significant symptoms, and the root length and dentin wall thickness continued to increase.

At present, stem cell therapy is mostly in the experimental research stage, and the clinical application effect is not stable. The most common scaffold materials currently used in clinical practice are blood clots (BC), platelet rich plasma (PRP), platelet rich fibrin (PRF), and combinations of blood clots with collagen membranes or membranes with different materials, with a success rate of 80-90% . Wikstr ö m A et al. reported that only 60% of cases showed improvement in clinical symptoms and radiological signs, as well as sustained root development, 11% had root growth, 30% had dentin thickening, and some cases failed due to failure to bleed and secondary infections.

7. Conclusion and expectation

The findings of this review highlight the significant potential of pulp regeneration to transform clinical practices, offering a promising approach to continue root growth and enhance root resistance following pulp necrosis. For young permanent teeth, apexification and pulp revascularization surgery can be used. The latter has better results and a higher success rate than the former. For mature permanent teeth, irreversible pulpitis causes complete destruction of pulp tissue, while the root tip lacks stem cells and dental papilla that can be self-repaired by the tissue. Therefore, exogenous introduction of scaffolds loaded with stem cells and growth factors can be used to promote the formation of pulp vascular like tissue in the root canal and reduce inflammation. However, stem cell therapy is currently in the experimental research stage and has achieved relatively good results in a few clinical applications.

In addition to the dental pulp regeneration strategies introduced in this article, current researchers have also found that extracellular vesicles and cell loaded microspheres have good prospects in dental pulp regeneration. Researchers implanted the extracellular vesicles of dental pulp stem cells with collagen membrane and dentin subcutaneously in nude mice, and immunohistochemistry showed the generation of dental pulp like tissue and high expression of vascular factors.

Cell loaded microspheres are a type of microsphere scaffold material with a diameter of 100-400um that can carry stem cells. Compared to traditional scaffolds, the specific surface area of microspheres is larger, significantly increasing the space for cell adhesion and growth. Research has shown that microspheres loaded with dental pulp stem cells can produce more dental pulp like tissue. In order to promote standardization and optimization of pulp regeneration treatment, future research needs to focus on developing unified induction protocols and evaluation tools. This will not only improve the predictability and success rate of treatment, but also provide patients with safer and more effective treatment plans. By synthesizing the current body of knowledge, this review aspires not only to inform clinical practices but also to catalyze advancements that will lead to improved patient outcomes in endodontics.

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