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Review Article

Current and future options for dental pulp therapy☆

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SUMMARY

Dental pulp is a connective tissue and has functions that include initiative, formative, protective, nutritive, and reparative activities. However, it has relatively low compliance, because it is enclosed in hard tissue. Its low compliance against damage, such as dental caries, results in the frequent removal of dental pulp during endodontic therapy. Loss of dental pulp frequently leads to fragility of the tooth, and eventually, a deterioration in the patient's quality of life. With the development of biomaterials such as bioceramics and advances in pulp biology such as the identification of dental pulp stem cells, novel ideas for the preservation of dental pulp, the regenerative therapy of dental pulp, and new biomaterials for direct pulp capping have now been proposed. Therapies for dental pulp are classified into three categories; direct pulp capping, vital pulp amputation, and treatment for non-vital teeth. In this review, we discuss current and future treatment options in these therapies.

1. Introduction

Dental pulp, surrounded by dentin, supports tooth vitality through the supply of essential factors via apical foramen and plays a key role in tooth maintenance [1]. Through the apical foramen, blood vessels supply nutrients and remove waste products, and the neural network indicates the presence of harmful stimuli through pain [2]. Various immune cells in the pulp including dendritic cells, macrophages, and T-lymphocytes prevent the invasion of microorganisms and other foreign antigens [2]. When sound dentin has been lost due to tooth wear, fracture, or caries, odontoblasts or odontoblast-like cells repair the tooth by depositing tertiary dentin, which is reactionary and reparative dentin, on the pulp chamber surface [2].

After the progression of dental caries and/or tooth fractures in a tooth crown, a bacterial infection and subsequent inflammatory response of dental pulp occurs, and the internal pressure in the pulp chamber significantly increases, resulting in pulp tissue ischemia with severe pain [2]. To release patients from the pain and eliminate infection of dental pulp, dentists eventually remove dental pulp by pulpectomy [3]. If pulpectomy is not performed, ischemia develops through impaired blood circulation, followed by pulp necrosis and periapical disease [4].

Resistance to external stimuli decreases in non-vital teeth due to complete loss of perception and immune functions, and the teeth become fragile due to loss of metabolic capacity [3]. Additionally, a non-vital tooth is immunocompromised and often re-infected by bacteria. Loss of sensation when the re-infection occurs can enable the progression of dental caries. The success rate of root canal retreatment is not high [5–8], and it is often necessary to repeat root canal treatment. Repetition of root canal treatment makes teeth more fragile and leads to cracking and/or fracture of the roots. As a result, the tooth has to be extracted, leading to a deterioration in the quality of life.

It is believed that a lot of root canal treatments and tooth extractions could be avoided if the proper direct pulp capping is carried out or pulp regeneration therapy is developed. This review will focus on potential approach for dental pulp preservation and regeneration therapies.

2. Current trends and perspectives of direct pulp capping

Untreated exposure of pulp to the oral cavity is the cause of pulpitis and pulp necrosis [9]; direct pulp capping or pulpotomy are clinically carried out in order to avoid pulp death. Direct pulp capping with dental materials is used to treat exposed vital pulp to facilitate the formation of reparative dentin. Generally, the most

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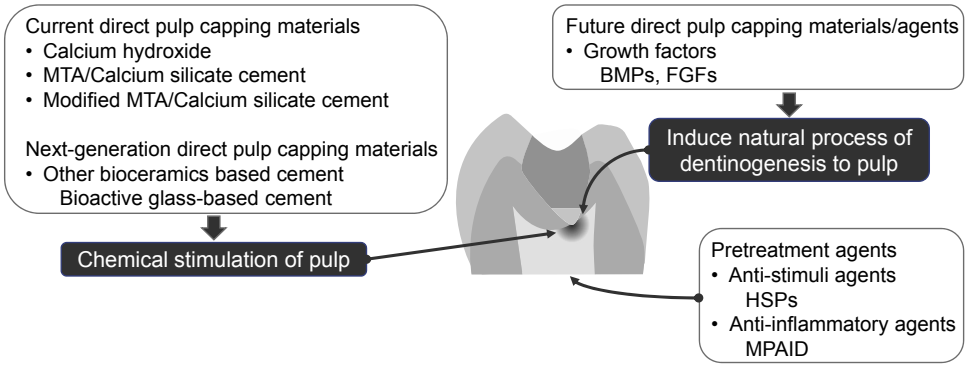

Figure 1. Current and future direct capping materials/agents.
Current direct pulp capping is the reaction of dental pulp to the chemical stimulation. Ideal direct pulp capping materials/agents is inducing dentinogenesis similar with natural biological process to pulp. Application of anti-stimuli and/or anti-inflammatory agents in combination with the direct pulp capping materials/agents will be affective.

widely used direct pulp capping agents are calcium hydroxide and mineral trioxide aggregate (MTA). In this section, we will focus on current and future direct capping materials/agents (Fig. 1).

2.1. Calcium hydroxide as a direct pulp capping material

Calcium hydroxide has been traditionally considered the "gold standard" of direct pulp capping materials and has been used for several decades [10]. Calcium hydroxide has a high pH of approximately 12, which provides excellent antibacterial properties [10]. Additionally, this high pH induces necrosis and mineralization directly beneath the material [11,12].

Calcium hydroxide materials are classified into 2 types: one-paste non-setting type and two-paste self-setting type. The major disadvantages of one-paste non-setting type calcium hydroxide systems are their lack of setting, weak physical properties, and gradual dissolution [9]. To improve these disadvantages, a curable two-paste (base/catalyst paste) calcium hydroxide system was developed and widely used. However, hardened materials show solubility, which may lead to the formation of dead space and microleakage [13,14]. In addition, two-paste calcium hydroxide exhibits more cytotoxic effects than do non-setting one-paste calcium hydroxide systems [15], possibly due to their additional components, including disalicylate, accelerator, and/or plasticizer [16]. Both types of calcium hydroxide materials induce heterogeneous dentin bridge formation with tunnel defects [9,17]. Tunnel defects in the dentin bridge fail to provide barriers, which are ideal biological sealants against bacterial infection.

2.2. Mineral trioxide aggregate (MTA) as a direct pulp capping material

MTA is known as one of bioactive materials in endodontics [18]. In recent years, MTA has been widely used as a direct pulp capping material. MTA includes a Portland cement component and shows antibacterial activity through the release of calcium hydroxide, which explains the similar action with the calcium hydroxide paste [19]. In addition, MTA has higher sealing ability, lower solubility, higher physical strength and stability than calcium hydroxide [9,20,21]. Further, MTA can set in a moist environment, prevent bacterial infiltration, and produce thicker dentin bridge formation with a lesser inflammatory response, less hyperemia, and less necrosis of pulp tissue compared to calcium hydroxide [21–25]. Many clinical reports demonstrated that the success rate of direct pulp capping was higher with MTA than with calcium hydroxide [26–30]

On the other hand, it has been reported that MTA shows several disadvantages; discoloration [26], the presence of toxic elements such as arsenic [31], higher cytotoxicity in its freshly mixed state [32], high pH during setting [33], poor handling [34], long setting time [35], and requirement of sufficient moisture during hardening [36,37].

2.3. Improved MTA/calcium silicates materials for direct pulp capping

Several MTA-derived materials have been provided in order to overcome the disadvantages of original MTA [35,38–40]. For example, the addition of calcium chloride to MTA resulted in a lower setting time and good biocompatibility [41], and replacing the Portland cement component in MTA with pure tricalcium silicate resulted in a biomaterial with improved physico-mechanical properties [42].

Light-curable resin-modified calcium-silicate based materials have also been developed. Compared to conventional MTA materials, the resin-modified light-curable cement has several advantages; immediate light-polymerization, prevention of materials washing out, and superior physical properties [43]. However, it is reported that the resin-modified light-curable MTA cement showed more cytotoxic than resin-free calcium silicates/MTA [15]. The clinical reports about these improved MTA/calcium silicates materials are insufficient. Further research is needed to evaluate these new materials for use in direct pulp capping.

2.4. Potential of bioactive glass-based cement for direct pulp capping

On one side of the favorable therapeutic result, it was reported that calcium silicates-based materials, including MTA, contain trace amounts of heavy metals [44], and some of them contain non-negligible amounts of arsenic [31]. An ideal pulp capping material should adhere to tooth substrate; maintain a sufficient seal; be insoluble in tissue fluids, dimensionally stable, non-resorbable, nontoxic, non-carcinogenic, non-genotoxic, and radiopaque; and exhibit biocompatibility and bioactivity [45–47]. No material currently available satisfies all desirable properties for direct pulp capping materials [47].

Bioactive glasses, one of the bioceramics comprised of silica (SiO_2), sodium oxide (Na_2O), calcium oxide (CaO), and phosphorus pentoxide (P_2O_5), are well-studied biomaterials [48]. Because bioactive glasses show a clinical ability to bond with bone through the formation of a hydroxyapatite layer on the surface [49,50], they have been used in the field of orthopedic surgery for bone engineering [51,52]. We hypothesized that bioactive glasses could be used in dental treatment, and we have recently developed bioactive glass-based cement [53]. The prototype of the bioactive glass-based

cement exhibited hydroxyapatite-like precipitation on the surface of the hardened cement, a stable pH level, and biocompatibility, without exhibiting cytotoxic effects [53]. From this prototype, a newly bioactive glass-based root canal sealer (Nishika Canal Sealer BG; Nippon Shika Yakuhin Co., Ltd., Yamaguchi, Japan) has been developed and is now being commercially marketed. Furthermore, this cement has the ability to induce reparative dentin formation on the surface of exposed dental pulp when it is applied as a direct pulp capping agent [54]. We are now focusing on the development of an improved version of bioactive glass-based cement as a direct pulp capping material.

2.5. Future direct pulp capping materials

Regardless of which materials are used in present methods of direct pulp capping, the mechanism of reparative dentin formation is a reaction of dental pulp to the chemical stimulation of materials with a high pH, unlike the process of dentin-pulp complex formation. The development of a novel therapy that induces wound healing and dentinogenesis similar to the natural process is expected.

Growth factors are candidates for direct pulp capping agents [55]. Bone morphogenetic protein (BMP)-2, a member of the Transforming growth factor (TGF)-β super family, has been approved by the US Food and Drug Administration (FDA) for clinical use, such as oral maxillofacial surgery [56]. BMP-2 is known to induce differentiation of dental pulp stem cells into odontoblasts [57]. Previous studies demonstrated that BMP-2 has induced expression of dentin sialoprotein and dentin matrix protein-1, differentiation markers of odontoblasts [58,59], and activated Smad signaling pathway, one of the intracellular signal transduction mechanism to regulate the cell proliferation, differentiation, or other function, involved in the induction process in the odontoblastic cell line [60–62]. Besides BMP-2, other BMP family members such as BMP-4, -6, -7, and growth/differentiation factor (Gdf)-11 were indicated as important growth factors to induce dentinogenesis [63,64]. Besides BMPs, TGF-β1 plays a crucial role in odontoblast differentiation [65], and fibroblast growth factor (FGF)-2 has also been demonstrated to regulate odontogenesis and is released during pulp wound healing [66,67].

During the direct pulp capping procedure, dentists administer local anesthetics and perform cavity preparation, which can cause adverse effects, including damage to dental pulp. The major adverse effects of these procedures are heat stress and ischemia. Heat stress is produced by the rotary cutting instruments used to remove infected dental hard tissue and is one of the most severe exogenous stimuli for dental pulp [2,68]. Ischemia caused by local anesthetics [69–71] may induce hypoxia and starvation in dental pulp [72,73]. We previously showed that pulp cells have the capability to resist heat stress and ischemia [74,75] and that the combination of heat stress and starvation reciprocally reinforces the stimulations [76,77]. We also demonstrated that pre-treated odontoblastic cells with the fever-range heat stress (41 °C) survived with odontoblast-like properties after lethal heat stress, with the accumulation of heat shock proteins (HSPs) and the cell-cycle arrest [78]. Accumulation of HSPs and cell-cycle arrest induce cellular resistance to various stimuli [79–84]. Our studies suggest that HSPs may also be one of biological molecules to be considered as pretreatment agents for direct pulp capping.

How to regulate inflammation is also important for preserving dental pulp. Recently, we found that a macromolecular translocation inhibitor II (MTI-II) peptide anti-inflammatory drug (MPAID) may regulate the inflammatory response and maintain a protective response of dental pulp [85]. MTI-II, small nuclear acidic protein, was previously demonstrated to be an enhancer of the transcriptional activity of glucocorticoid-bound glucocorticoid receptor, and MPAID was bioengineered from the structure of MTI-II as an inhibitor of NF-κB transactivation [86–88]. Anti-inflammatory agents similar to MPAID could be candidates for direct pulp capping or pretreatment agents.

3. Dentin-pulp complex regeneration following pulpotomy

Pulpotomy is a therapy performed on coronal partial inflamed pulp in order to avoid pulpectomy. In this section, we propose a novel strategy for dentin-pulp complex regeneration therapy performed after pulpotomy.

3.1. Problems in current pulpotomy

In the procedure of pulpotomy, coronal pulp is amputated surgically, and the surface of remaining root pulp is treated with a medicament such as calcium hydroxide or MTA at the root canal orifice in order to promote the formation of a dentin bridge [3,89]. A newly formed dentin bridge is porous hard tissue with a low degree of calcification [17,90]. The most important issue is that current pulpotomy never leads to the regeneration of the dentin-pulp complex that was lost in the coronal portion.

3.2. Novel strategy for local regeneration of the dentin-pulp complex following pulpotomy

It is well known that the induction of stem cells and capillary networks, the delivery system of growth factors, and scaffolds for cell proliferation and differentiation are essential for tissue regeneration [91,92]. For dentin-pulp complex regeneration following pulp amputation, it is possible to induce dental pulp stem cells and capillaries from the residual root pulp tissue and prepare a closed space using adhesive materials. Critical points include the choice of growth factor(s), delivery system of growth factor(s), and a suitable scaffold in order to induce stem cells and blood vessels from the residual pulp.

In previous research on dentin-pulp complex regeneration in rat amputated pulp, we used FGF-2 as the growth factor, gelatin hydrogels as the delivery system of FGF-2, and collagen sponges as the scaffold. FGF-2 is known to play important roles in the physiologic conditions of odontogenesis [93,94] as well as pathologic conditions [95–97]. Gelatin hydrogels have been developed for gradual and continual release of growth factors [98–101]. It has been demonstrated that the controlled release of FGF-2 from gelatin hydrogels induces the regeneration of angiogenesis [102], bone [103–105], periodontal tissues [106], and other tissues [107–109]. Collagen is a major macromolecular constituent of the dentin extracellular matrix (ECM) with excellent biocompatibility, and it is the most extensively studied naturally occurring material for dental tissue engineering [110]. We implanted FGF-2-incorporated gelatin hydrogel with collagen sponge on the amputated pulp surface of a rat upper first molar and found that controlled release of FGF-2 from gelatin hydrogel induced regeneration of pulp tissue and osteo-dentin-like hard tissue in the defect area [111,112]. These results suggest that the combination of FGF-2, gelatin hydrogels, and scaffolds may induce the local regeneration of the dentin-pulp complex after pulpotomy.

However, the induced dentin in previous studies did not have an ideal structure with dentinal tubules, and its quantity was insufficient for protecting the dental pulp or withstanding bite forces. These weak points should be overcome before clinical application. BMP-2 may be useful due to its demonstrated ability to induce *in vivo* dentin formation after pulpotomy [113], and other growth factors involved in dentinogenesis are also candidates, as mentioned before. Platelet-rich plasma (PRP) including growth factors

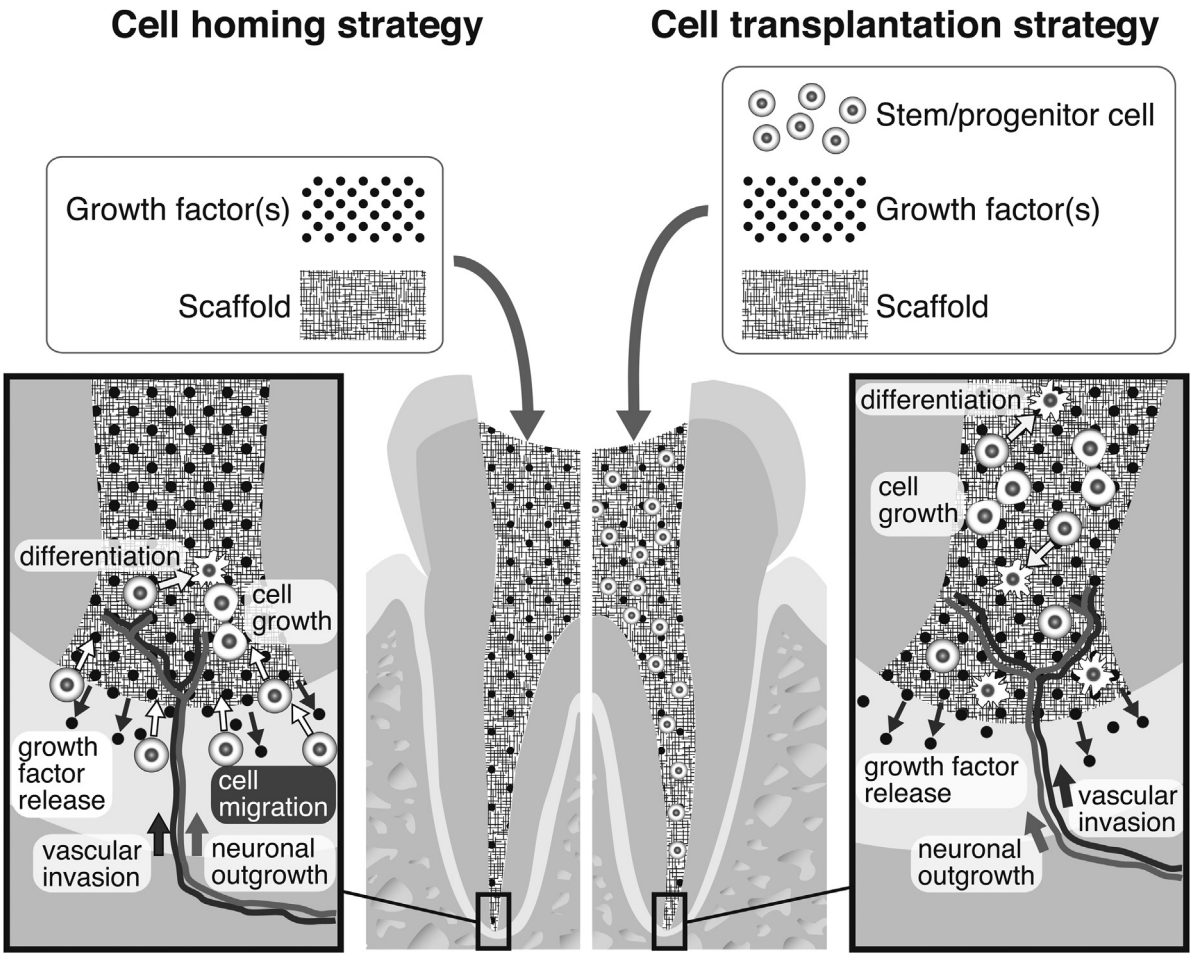

Figure 2. Two strategies for pulp regeneration therapy to non-vital mature permanent tooth.
In the cell homing strategy, growth factor(s) and scaffold are implanted into root canal. Released growth factor(s) from root canal induced stem/progenitor cell migration, vascular invasion, and neuronal outgrowth from periapical tissue. In the cell transplantation strategy, stem/progenitor cells are injected into root canal with growth factor(s) and scaffold. Released growth factor(s) induced vascular invasion and neuronal outgrowth from periapical tissue into the root canal.

is also a potential material; we found that it enhances differentiation of odontoblastic cells and alkaline phosphatase activity [114]. These results suggest that the suitable combination of growth factors or PRP may induce local regeneration of ideal dentin-pulp complex.

We sought a further suitable scaffold for the dentin-pulp complex regeneration therapy following pulpotomy. Besides collagen, several natural polymers, such as chitosan and gelatin, and synthetic polymers, such as D, L-lactide and glycolide (PLG) and polyglycolic acid (PGA), were exhibited to be used for the therapy [115–117]. Hyaluronic acid (HA), one of the glycosaminoglycans that are widely distributed in the human body, is known to play important roles in maintaining morphologic organization and anti-inflammatory effects [118,119], and is reported to be well-suited for tissue engineering material [120–124]. To clarify whether HA sponge is useful as a scaffold for dentin-pulp complex regeneration therapy, we carried out *in vitro* and *in vivo* studies and found that HA sponge has ideal properties to do so [125].

Unlike immature teeth with abundant blood flow and cells, local regeneration of the dentin-pulp complex following pulpotomy in mature teeth may be difficult. However, identification of the perfect combination of growth factors and the development of a delivery system for growth factors and scaffolds for cells would progress local regeneration therapy of dentin-pulp complex following pulpotomy [126].

4. Dentin-pulp complex regeneration therapy for non-vital teeth after pulpectomy or pulp necrosis

The ultimate goal for endodontists or dentists is the regeneration of dental pulp for non-vital teeth after pulpectomy or pulp necrosis. In this section, we will discuss the possibility of pulp regeneration therapy for non-vital teeth.

4.1. Revitalization/revascularization for non-vital, immature permanent teeth

Recently, a clinical protocol for the root revitalization/revascularization of non-vital immature permanent teeth has been introduced. In this protocol, a broach is inserted into the root canal in order to make the blood rise from the vessels of periapical tissue, followed by filling of calcium hydroxide or MTA on the blood clot residing in the root canal to recover vitality and root development [127]. However, it has been demonstrated that newly produced hard tissue at the end of the root by this protocol is not dentin-like but cementum-like and similar to periodontal ligament connective tissues [128]. Therefore, conventional revitalization/revascularization methods could not regenerate dentin-pulp complex. To lead true dentin-pulp complex regeneration by revitalization/revascularization, suitable scaffolds and growth factors which can induce the differentiation of dental

pulp cells containing odontoblast and dentin formation would be needed to apply into root canal, in addition to the induction of clot fibrin and cells from dental papilla or periodontal tissue.

4.2. Pulp regeneration for non-vital mature permanent teeth

To achieve the entire dental pulp regeneration for non-vital mature permanent teeth, major two strategies are utilized in dental research; the cell homing strategy and the cell transplantation strategy (Fig. 2).

The cell homing strategy is achieved by the induction of stem/progenitor cells from periapical tissue around the apical area of the root. In this strategy, scaffolds impregnated with growth factors are injected into root canals to induce migration, proliferation, and differentiation of endogenous stem/progenitor cells residing around the root apex, through enlarged apical foramen [129]. The cell homing strategy might be easier to perform in a clinical setting than the cell transplantation strategy due to its cell-free approach, as there is no need to isolate or manipulate stem cells *in vitro* [129]. Unlike in immature teeth, there are no dental papilla cells that possess pluripotency in mature teeth. This strategy may rely on establishment of methods inducing stem cells residing around the root apex, for example, periodontal ligament stem cells.

The cell transplantation strategy is expected to realize a high success rate of dentin-pulp complex regeneration. To achieve this strategy, establishment of stem cell sources is essential. Dental pulp stem cells (DPSCs) were shown to exhibit the ability to form ectopic human dentin-pulp complex-like structures [130–132]. Recently, Nakashima et al. succeeded and reported the human dental pulp regeneration therapy by autologous transplantation of DPSC into pulpectomized teeth in 5 patients with irreversible pulpitis [133]. Besides DPSCs, several other types of stem cells or progenitor cells from dental tissues have been isolated and characterized, such as stem cells from human exfoliated teeth (SHED) [134], periodontal ligament stem cells (PDLSC) [135], stem cells from apical papilla (SCAP) [136], and dental follicle progenitor cells (DFPC) [137]. DPSCs, SHED, and SCAP are potentially suitable cell sources for dental pulp regeneration, because they are derived from pulp tissue or the precursor of pulp. The sources of these cells are extracted third molar or teeth for the purpose of an orthodontic, or extracted inflamed dental pulp [138]; however, these are very limited. For cell transplantation, exploration of other stem cell sources is important. A PDLSC was demonstrated to have the ability to differentiate into an odontogenic lineage cell [139]. Bone marrow derived mesenchymal cells (BMSCs), human bone marrow stromal cells (HMSCs), and adipose tissue derived mesenchymal stem cells (ADMSCs) are alternative source candidates [139,140]. It has also been demonstrated that induced pluripotent stem (iPS) cells are able to differentiate into dental mesenchymal cells *in vitro* and form dentin- and dental pulp-like structures *in vivo* [141,142].

In order to provide a sufficient number of cells similar to the off-the-shelf component at the time of treatment, establishing a dental stem cell banking system is essential. This establishment allows generalization of pulp regeneration therapy in endodontic therapy.

5. Conclusion

In this review, we discussed current and future endodontic therapies. Most current endodontic procedures are irreversible and sacrifice hard and soft tissue, making teeth vulnerable. Thanks to great strides in the field of biology and the development of biomaterials, new biological pulp capping agents and strategies of regeneration therapies will be realized over the next few decades. Although many more studies are required, the treatment options presented here will change endodontic therapies and improve quality of life in patients.

Conflict of interest statement

None declared

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