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Tissue Engineering Scaffolds for Dentin-Pulp Complex Regeneration

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ABSTRACT

The primary challenge confronting modern regenerative endodontics resides in preserving pulp tissue vitality and restoring the dentin-pulp complex, achievable solely through the integration of cellular engineering. This medical discipline relies on an effective combination of three principal components: scaffolds, stem cells, and growth factors. The Scaffold is a three-dimensional matrix providing primary structural support during tissue regeneration. Its pivotal role in creating an optimal environment for cellular proliferation and subsequent differentiation underscores its significance for tissue engineering success. Scaffolds are classified into two broad categories based on their source: natural and synthetic materials, each exhibiting distinct biological and mechanical properties. Naturally derived materials typically demonstrate they enhanced bioactivity and biocompatibility, whereas synthetic counterparts have superior mechanical attributes and greater quantitative availability. Across various medical domains, researchers persist in harnessing the potential of both material types through experimental and preclinical investigations, striving to mitigate inherent shortcomings through material hybridization. The field of regenerative endodontics is no exception to this pursuit.

Keywords: Pulp-dentin complex; regenerative endodontics; scaffolds.

INTRODUCTION

The Scaffold functions as a three-dimensional microenvironment crucial for stem cell activities, facilitating cell adhesion, infiltration, differentiation, and proliferation. Additionally, it modulates stem cell metabolism through the actions of growth factors. Throughout the regeneration process, it facilitates the absorption of oxygen and nutrients.[1]

Presently, a diverse array of scaffolds is available for dentin-pulp complex restoration. However, selecting the ideal material proves challenging due to the extensive list of requirements. he Scaffold must exhibit safety, non-toxicity (regarding degradation products), biocompatibility, low immunogenicity, microporosity, and the ability to promote cell proliferation while being degradable (temporarily serving its function before being replaced by newly formed tissue).[1]

Scaffolds utilized in regenerative endodontics encompass natural (such as chitosan, alginate, hyaluronic acid, and gelatin) and synthetic (including ceramics and composites) materials. Notably, scaffolds compatible with combination approaches involving other materials are preferred.[2]

This article discusses the characteristics of primary scaffolds that, based on preclinical and experimental studies, have demonstrated varying degrees of success in dentin-pulp complex restoration.

REVIEW

Chitosan

Chitosan, a natural polysaccharide derived from chitin sourced from fungi, insects, and crustacean shells,[3] exhibits commendable biological properties. These include high biocompatibility, low cytotoxicity, biodegradability, antimicrobial effects against gram-negative and gram-positive bacteria, including E. feacalis,[4,5] as well as fungostatic action, non-carcinogenicity, and hemostatic ability. Additionally, it promotes cell adhesion, proliferation, and differentiation.[6] Despite its resistance to bacterial enzymes, attributed to the mechanical stability of its nanoparticles, chitosan's noteworthy polycation content and highly crystalline structure may limit its efficacy when used independently. Typically, chitosan is employed solely in the form of injectable hydrogels. Moreover, it is commonly used with polymers and other biomaterials.[7] An advantageous attribute of chitosan is its high affinity for binding growth factors, DNA, and glycosaminoglycans.[8]

Numerous experimental studies have investigated the efficacy of chitosan in dentin-pulp tissue restoration. In one study, combining chitosan with cellularized fibrin hydrogel significantly augmented the antibacterial effect and enhanced dental pulp regeneration rates.[9] Another study demonstrated that combining chitosan with a 2% calcium silicate suspension increased scaffold diameter and elevated calcium and odontogenic marker expression from human

dental pulp.[10] Chitosan has also been explored in Regenerative Endodontic Procedures (REPs). Although mixing chitosan with blood stimulated the formation of histologically confirmed new soft tissue, it did not induce mineralized tissue formation around the pulp.[11] In another investigation, the combination of carboxymethyl chitosan-based scaffold (CMCS) with TGF-β1 exhibited notable migration of stem cells from the apical papilla (SCAP) and enhanced odontogenic marker expression within 24 hours in vitro compared to TGF-β1 alone. CMCS, being water-soluble and SCAP-compatible, improved dentin surface properties, enhancing antibacterial efficacy and ultrastructural stability. Researchers concluded that the CMCS-TGF-β1 combination enhanced SCAP viability, migration, and odontogenic differentiation, suggesting its promise for SCAP-mediated Regenerative Endodontic Therapy (RET).[12] Chitosan's Scaffold fosters a conducive microenvironment for the bioactivity of dental pulp stem cells (DPSC).[13,14] Animal studies have demonstrated that chitosan loaded with DPSCs and growth factors regenerated pulp-dentin-like tissue and achieved apexification in young permanent teeth with periapical lesions.[15] However, contrasting results were observed in another animal study where chitosan failed to induce intraductal hard and soft tissue formation compared to blood clots in REPs.[16]

Alginate

Alginate, derived from the cell wall of brown algae (Phaeophyceae) or certain bacteria such as Pseudomonas and Azotobacter, is prized in tissue engineering for its high biocompatibility, favorable immunogenicity, gelation properties, and cost-effectiveness.[17] The gelation behavior of this biopolymer hinges on calcium ion exchange and/or the surrounding environment's low pH. Calcium content enhances cross-link density, bolstering alginate's mechanical strength.[18,19] Its polyvalent cation content facilitates cell immobilization, rendering it suitable for use as a hydrogel in combination with other materials. Some authors suggest that its utility in Regenerative Endodontic Procedures (REP) is limited, necessitating its combination with other materials, such as bioactive polymers, to enhance efficacy.[20,21]

Alginate hydrogel loaded with stem cells finds active application in regenerative endodontics, both in conjunction with growth factors and in their absence. An experimental study conducted in 2002 demonstrated that alginate loaded with the growth factor TGF-β1, when applied to tooth enamel, could induce the differentiation of odontoblast-like cells and promote the formation of tubular dentin.[22] Furthermore, in 2006, an experiment conducted by Fujiwara et al. illustrated that stem cells isolated from rat dental pulp, when combined with alginate, induced the differentiation of odontoblast-like cells and subsequent calcification. Additionally, the same study revealed that the addition of beta-glycerophosphate to alginate led to the release of mRNA for dentin sialoprotein (DSP) and dentin phosphoprotein (DPP), along with an increase in alkaline phosphatase levels, serving as early markers of odontoblast differentiation.[23] Zhang et al. and their colleagues developed an injectable alginate hydrogel embedded with microspheres encapsulating human pulp stem cells (hDPSCs) and vascular endothelial growth factor (VEGF). Their experiment showcased the regeneration of pulp-like tissue.[24]

While alginate holds significance in various domains of tissue engineering, its drawbacks, including low mechanical strength and unpredictable biodegradation rates, render it less ideal for Regenerative Endodontic Procedures (REP). However, the incorporation of nano-hydroxyapatite into alginate gel serves to mitigate these limitations to some extent. This addition enhances mechanical properties and bolstering strength while concurrently promoting the differentiation and mineralization of human dental pulp stem cells (hDPSCs).[25]

Hyaluronic acid

Hyaluronic acid (HA) is a polymer of disaccharides commonly found within connective, epithelial, and nerve tissue scaffolds. Notably, it is present in human dental pulp tissue, where it serves a pivotal role in preserving intercellular distance and morphological integrity while also contributing to the modulation of dentin and enamel matrix during odontogenesis.[26] HA is synthesized from D-glucuronic acid and N-acetyl-D-glucosamine. The clinical appeal of HA stems from its liquid injectable form, enabling rapid fixation, optimal adaptation, and gelation within the intricate morphology of the canal system.[27,28] HA and scaffolds derived from it offer numerous advantages, including biocompatibility, biodegradability, non-immunogenicity, non-thrombogenicity, hydrophilicity, and a porous architecture akin to the pulp-dentin scaffold.[29,30] Notably, its three-dimensional structure fosters an environment conducive to blood vessel proliferation and stem cell differentiation.

In cell-free Regenerative Endodontic Therapy (RET), the primary function of the Scaffold is to mobilize endogenous stem cells from the periapical tissue. Hyaluronic acid (HA) interacts with the membrane receptor CD44 on Stem Cells from the Apical papillae (SCAPs), thereby inducing their migration into the root canal space. Cultivating SCAPs in HA-based hydrogels promotes their differentiation and mineralization.[31] Ferroni et al. demonstrated that Dental Pulp Stem Cells (DPSCs), in conjunction with other growth factors, when encapsulated within an HA-based matrix, differentiate into neural, glial, osteogenic, and endothelial cells, ultimately forming dentin-pulp-like tissue.[32] Additionally, in 2014, Pardue et al. proposed that degradation products of HA may contain proangiogenic

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growth factors, which play a pivotal role in tooth tissue regeneration via revascularization.[33]

Inuyama and colleagues conducted an experiment wherein they applied a 3D cloud of hyaluronic acid (HA) to cover the exposed pulp. This intervention formed a reorganized tissue rich in cells along the perimeter of the amputated pulp.[34] Similarly, Silva investigated an HA hydrogel enriched with platelet lysate and augmented with cellulose nanocrystals (CNCs). The incorporation of CNCs notably bolstered the mechanical properties of HA, enhancing its resistance to hydrolysis and enzymatic degradation while augmenting cell mobilization and proangiogenic potential.[35]

However, HA does have drawbacks for pulp-dentin complex restoration, including its relatively low mechanical strength and the necessity of combining it with growth factors such as BMP-2 and TGF-B1. A potential complication of HA is the risk of hypersensitivity reactions to bacterial impurities.[36]

Collagen

Collagen is the primary structural protein within the Scaffold of mammalian connective tissue, rendering it one of the most extensively studied materials in this domain.[37] Among collagen types, collagen type I predominates in tissue engineering applications due to its propensity for promoting the proliferation and mineralization of Dental Pulp Stem Cells (DPSCs) compared to other collagen types.[38,39] Noteworthy characteristics of collagen type I include its porous structure, high biocompatibility, and bioactivity, facilitating cell adhesion, migration, and proliferation. It undergoes biodegradation through the action of collagenase enzymes. Despite collagen's inherent weak mechanical properties, it is deemed an acceptable material for pulp tissue regeneration, as it closely resembles pulp tissue in terms of viscoelastic properties.[40]

In Regenerative Endodontics, collagen is employed in its pure form (e.g., collagen sponge, membrane, pellet) and in combination with other natural or synthetic materials.[41-44] Although combining cross-linked collagen with other materials may enhance its mechanical and physical properties, there exists a risk that the addition of chemical agents may compromise biocompatibility and cell proliferation capacity.[45]

Sumita and colleagues conducted an in vivo study comparing the potential of collagen foam as a three-dimensional scaffold in regenerative dentistry to polyglycolic acid. Their research demonstrated a significantly superior potential for tooth formation with the collagen sponge.[46] Prescott et al. evaluated the efficacy of a collagen scaffold loaded with dental stem cells (DPSCs) and dentin matrix protein 1 (DMP1) in regenerating dentin-pulp-like tissues in mice. Their findings indicated that this combination could generate an organized matrix of pulp-like tissue.[47] Nosrat et al. conducted a clinical study on non-infected immature first premolars in three patients. They compared the intracanal performance of SynOss™-bovine collagen type I and synthetic carbonate apatite. Histological examination revealed the formation of cement-like mineralized tissue on dentin walls after 2.5-7 months, attributed to the combined action of SynOss™ and the blood clot. Treatment with SynOss™ alone resulted in radiographically confirmed asymptomatic periapical lesions without intracanal wall thickening. Furthermore, fibrous tissue in the intracanal space and reparative cement formation on dentin walls were observed solely in the presence of the blood clot. Notably, the combination of collagen type I, blood clot, and dental stem cells facilitated complex tissue formation within the canal, surpassing outcomes achieved with the blood clot alone.[48]

Gelatin

Gelatin, a biopolymeric protein derived from the partial hydrolysis of collagen, exhibits a composition similar to its precursor, collagen. Its capability to promote the proliferation and differentiation of odontoblasts underscores its significance in dentistry.[49] Classified as a hydrogel, gelatin finds application in various fields, including food products, cosmetics, tissue engineering as a carrier, and facilitating cell adhesion in culture.[50] Comparative studies between gelatin and hydrogel gelatin reveal superior biocompatibility of the hydrogel form, attributed to its lower immunogenicity.[51] Gelatin is susceptible to degradation and highly sensitive to temperature fluctuations.[52]

Proteins and Peptides

Recently, a novel subgroup of peptides and proteins has emerged within the classification of scaffolds. These materials offer significant advantages, including biocompatibility and biodegradability. Moreover, their main strength lies in the versatile potential for modification, which allows for manipulating their physical, chemical, and biological characteristics.[53]

Fibrin

Fibrin, a naturally occurring biopolymer, is formed through the polymerization of fibrinogen in blood plasma, catalyzed by thrombin during blood coagulation. This forms a fibrous polymer network for hemostasis and wound healing.[54] Fibrin boasts several advantages, including biocompatibility, immunogenicity, cell adhesion, proliferation, ease of introduction into the root canal, and cost-effectiveness compared to other materials.[55,56] Rapid fibrin degradation occurs within a few days, and it is replaced by a Scaffold (ECM) released from cells with non-toxic byproducts.[57] However, fibrin's independent use in cell engineering is hindered by its weak mechanical properties, premature degradation, susceptibility to shrinkage, disease transmission risks (without autotransplantation), and lack of

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antibacterial activity.[58,59] Gel shrinkage can be mitigated using fixatives like K-lysine.[60] To enhance fibrin's structural and functional characteristics, it is often combined with various natural gels (e.g., alginate, chitosan, collagen, HA) and synthetic materials (e.g., polyethylene glycol, lactic acid, fibrin-based bio-ink for 3D printing).[61] Fibrin degradation by proteases (e.g., plasmin) and metalloproteinases further refine its properties.[62] Moreover, its characteristics can be modulated by polymerization conditions, environmental pH, calcium, fibrinogen, and thrombin concentrations.[63] Several promising experiments have utilized fibrin-based Scaffolds in regenerative endodontics. For instance, a 2021 publication by M. Ducret and colleagues confirmed the potential of fibrin-based hydrogel for dental pulp regeneration.[64] Additionally, an experimental study in 2020 by Jang G.H. et al. demonstrated odontoblast layer formation and pulp-like tissue growth in the root canal using fibrin-based materials.[65]

Decellularised ECM

Decellularized Extracellular Matrix (ECM) is acquired by eliminating cellular components from native tissues while preserving the natural ECM structure. The resultant ECM retains various growth factors, signaling molecules, and structural proteins pivotal for cell adhesion, proliferation, and differentiation. Complete preservation of ECM components is imperative during decellularization, thus emphasizing the critical role of optimizing decellularization methods. Various decellularization techniques have been adopted, including chemical detergents, enzymatic treatments, and mechanical action. Ideally, the decellularized ECM closely mimics the structure of the target tissue, facilitating cell infiltration, proliferation, differentiation, and tissue formation by mobilizing endogenous stem cells. Experimental implementation or attempts of decellularization have been witnessed in muscle tissue, submandibular salivary gland, trachea, cartilaginous tissue, and dental pulp for pulp-dentin regeneration.[66]

Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF)

Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) are autologous platelet concentrates prepared ex vivo by centrifuging the patient's blood. These platelet concentrates find applications across various medical fields, including plastic surgery, sports medicine, and dentistry. Their utilization is predicated on stimulating the regeneration process through the release of biologically active substances—growth factors from platelet granules, such as PDGF (platelet-derived growth factor), TGFb (tumor growth factor beta), IGFs (insulin-like growth factors), VEGF (vascular endothelial growth factor), EGF (epithelial growth factor), and ECGF (epithelial cell growth factor).[67,68] However, the use of PRP is constrained by the absence of standardized preparation protocols encompassing platelet concentration, precise storage duration, and varying polymerization strategies.[69,70] In contrast, PRF offers distinct advantages. Its preparation does not involve anticoagulant addition, facilitating slow polymerization that enhances growth factor release and cell migration.[71] Nonetheless, PRF must be utilized immediately after preparation due to its limited quantity and the risk of structural integrity loss.[72] Encouraging studies in regenerative endodontics have explored the use of PRP and PRF as Scaffolds.[73,74]

Synthetic polymers

Synthetic polymer materials offer distinct advantages, such as non-toxicity and biodegradability. Specific properties, including mechanical characteristics, viscosity, porosity, and physical and chemical attributes, can be precisely tailored during production. Manipulation of biochemical characteristics enables control over parameters like degradability rate, structural rigidity, microstructure, and porosity.[75-77] While enzymes predominantly degrade natural polymers, synthetic polymers undergo degradation through hydrolysis. However, intermediate hydrolysis products may alter pH towards acidity locally, potentially inducing chronic or acute inflammatory reactions.[78,79,80]

Synthetic polymer materials offer advantages in terms of scalability, cost-effectiveness, and extended shelf life.[81] Nonetheless, their hydrophobic nature limits bioactivity, constituting a primary drawback.[82] Among the most widely used synthetic polymers in tissue engineering are lactic acid (PLA), polyglycolic acid (PGA), and polylactide-co-glycolide (PLGA), all renowned for their non-toxicity and biodegradability.[83]

PLA and PGA are synthesized through the condensation of lactic and glycolic acids. Their intermediate breakdown products are natural metabolites excreted through the kidneys, their primary advantage.[84] However, concerns regarding the biocompatibility of these materials arise from the accumulation of their intermediates.[85]

PGA serves as a synthetic scaffold utilized for cell transplantation. Upon production of their extracellular matrix (ECM), cells facilitate the degradation of PGA. Various cell types have demonstrated adhesion and proliferation on PGA scaffolds, including dental pulp progenitor/progenitor cells, pulp fibroblasts, and ex vivo human pulp tissue cells. In rabbit and mouse xenograft models, PGA and PLA copolymers, in conjunction with dental pulp progenitor cells, facilitated the formation of pulp-like tissue.[86-88]

PLA has successfully formed dental pulp and periodontal tissues.[89] This material can potentially enhance the proliferation of dental pulp stem cells compared to collagen or calcium phosphate scaffolds. It is well-established that morphological characteristics of scaffolds, such as pore size and distance between struts, play a crucial role in influencing cell adhesion, proliferation, and differentiation.[90] 3D printing technology is leveraged to produce PLA scaffolds for pulp tissue engineering. Alksne and colleagues developed

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two types of 3D-printed PLA matrices—wavy and porous—promoting the proliferation of DPSCs.[91] In a study by Hsiao et al., PLA matrices with varying interstice sizes (150 µm and 200 µm) were compared, revealing that matrices with relatively narrow interstices could induce the differentiation of hDPSCs into neural tissue.[92]

PLA possesses adequate mechanical properties and undergoes degradation into carbon dioxide and water, yielding safe and non-toxic byproducts. PLLA, a frequently utilized isomeric form of PLA, shares similar advantageous characteristics.[93,94] PLA nanoparticles serve as effective antibiotic carriers. For instance, a fibrin hydrogel incorporating clindamycin-loaded PLA nanoparticles displayed antibacterial activity without compromising the viability and functionality of DPSCs.[95]

Stem cells derived from human primary teeth (SHED) implanted in PLA on a dentin disc led to the development of odontoblast-like cells, new dentin, and vascularized pulp-like tissue. In vivo, investigations by Huang et al. demonstrated that when SCAP stem cells and L-lactide, poly-D, and glycoside were introduced into empty canals, soft tissue resembling pulp formed, subsequently covered with new dentin tissue on the surface. However, it is worth noting that synthetic polymers, as mentioned earlier, may trigger both immediate and long-term inflammatory reactions.[96]

PLGA, a copolymer comprising two distinct monomers, comprises glycolic acid and lactic acid cyclic dimers. The ratio between these acids dictates the formation of PLGA with varying shapes and degradation times.[97] This synthetic polymer finds utility in dentistry for regenerating dentin-pulp tissue and is compatible with dental stem cells (DSCs). Mooney reported the generation of new pulp-like tissue through a combination of PGA and DPSCs.[98] Subsequently, Kuang et al. conducted a comparative assessment of the biocompatibility and biodegradability of PLA-based matrices, elucidating their regulatory role in pulp-dentin complex regeneration. In an in vivo experiment, PLA-based scaffolds exhibited a high capacity for DPSC proliferation and odontogenic differentiation, characterized by the secretion of ALP, osteocalcin, bone sialoprotein, collagen type I, and dentin sialoprotein genes. Histological analysis confirmed the formation of dentin-like tissue in vivo.[99] Additionally, PLGA matrices demonstrated enhanced proliferation and adhesion capabilities of DPSCs under microgravity stimulation, a procedure known to promote MSC growth.[100]

Hydrogels

Hydrogels represent injectable biomaterials known for their ease of use and excellent adaptability to the heterogeneous anatomy of root canal systems, making them highly sought-after for Regenerative Endodontic Procedures (REPs).[101] These materials consist of 3D hydrophilic polymer matrices or networks capable of absorbing substantial water and tissue fluid.[102] Notably, hydrogels exhibit high tunability and biocompatibility, rendering them remarkably akin to natural extracellular matrix (ECM).

Hydrogels are categorized into natural, synthetic, and hybrid types based on the source of the polymer chain. Hybrid hydrogels are produced by combining natural and synthetic materials. Hydrogels derived from natural polymers primarily utilize collagen, fibrin, chitosan, alginate, or hyaluronic acid, while synthetic hydrogels are formulated from PLA, PEG, or self-assembling peptides. Natural polymer-based hydrogels possess the capacity to mimic natural tissue but are susceptible to breakage due to their low mechanical properties. Conversely, synthetic hydrogels exhibit relatively higher mechanical properties and physicochemical characteristics but demonstrate less similarity to natural tissue.[103] Notably, hydrogels composed of self-assembling peptides create favorable microenvironments for cell adhesion and proliferation. Some hydrogel characteristics are modifiable to enhance cell migration and angiogenesis potential.[104]

The hydrogel form of scaffolds holds promising potential in regenerative endodontics. Active research is focused on developing scaffold hydrogels that meet appropriate criteria.

Bioceramic scaffolds

Bioceramic scaffold refers to materials encompassing glass ceramics, bioactive glass, and calcium/phosphate mixtures. Ceramic materials based on calcium phosphate are typically utilized most frequently due to their minimal toxicity, promotion of osteoclast activity and bone formation, and close resemblance to mineralized tissue. Calcium phosphate (CaP) scaffolds, such as tricalcium phosphate (TCP) and hydroxyapatite (HA), are commonly employed for bone regeneration purposes.

Bioceramic materials have several drawbacks, including extended production times, absence of organic components, heterogeneous particle size and shape, coarse grain structure, difficulty forming, dull appearance, slow degradation, high density, brittleness, and low mechanical stability. These limitations can be mitigated by combining bioceramic materials with polymeric Scaffolds.[105,106]

Composite Scaffolds

Composite scaffolds are formed through the amalgamation of biopolymer and bioceramic materials. Their effectiveness hinges on balancing the advantages and limitations inherent in each constituent component. Combining natural and synthetic materials achieves composite materials with enhanced characteristics. These matrices exhibit high biocompatibility, improved mechanical strength, and enhanced biological activity.[107]

Composite scaffolds hold promising potential for restoring the dentin-pulp complex. For instance, Chiu et al. implanted dental pulp stem cells (DPSCs) into a

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polycaprolactone hybrid 3D scaffold designed for bone tissue regeneration. Their findings revealed enhanced DPSC adhesion, proliferation, and differentiation with this composite combination.[108]

CONCLUSIONS

Despite the diverse materials discussed and their respective capabilities, identifying a single ideal scaffold for restoring the dentin-pulp complex remains challenging. Natural materials offer high biocompatibility, while synthetic counterparts boast favorable mechanical properties and controlled degradation rates. However, a comprehensive analysis of their characteristics and initial experimental investigations suggest that a blend of natural and synthetic materials is well-suited to meet the demands placed on the scaffolds for dentin-pulp complex restoration.

The ongoing advancement of 3D bioprinting technology holds promise for enhancing the properties and functionalities of these materials in the foreseeable future. Numerous preclinical studies will be necessary to identify the optimal scaffold combination that closely aligns with the ideal requirements. With collaborative efforts from biologists, biotechnologists, and clinicians, we anticipate that experimental in vivo and in vitro studies to restore the pulp-dentin complex will transition from laboratory settings to clinical practice soon.

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