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Review

Functional hydrogels for treatment of dental caries

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ABSTRACT

As the most popular teeth problem, dental caries can result in pain, suffering, impaired function, and diminished quality of life among communities, which calls for new strategies to improve the therapeutic effects. With suitable biocompatibility properties, functional hydrogels had developed dramatically in dental caries treatments. In this review, the occurrence and development of dental caries were introduced. Then, the current hydrogels toward dental caries with antibacterial or (and) remineralization properties and hydrogel-related dental pulp tissue engineering were summarized. Finally, the limitation and outlook of the applications of hydrogels on dental caries treatment were prospected. Exploring innovative hydrogel delivery systems will build a solid basis for a brighter future of more friendly, effective and personalized treatment to deal with dental caries.

1. Introduction

The oral cavity is the beginning of the digestive tract, with the functions of eating and language, playing a huge role in daily life [1]. Yet, various diseases ranging from infections to tumors can occur in the mouth [2], which bring suffering to human health and vitality. Among them, dental caries is the most prevalent problem of public health, considering the demineralization of dental tissue caused by bacterial infection [3,4]. During traditional invasive operations such as resin filling, shaking in the cavity preparation (to remove the decayed tissue) may make patients suffer from fear and pain. Hence, new strategies for comfortable therapy with minimal invasion were urgently anticipated [5]. With the development of materials, many scaffolds with antibacterial and remineralization effects were synthesized and applied, bringing brightness to dental caries treatment [6–8]. Combined with traditional medicine or newly developed drugs, these materials have shown promising potentials in strategies ranging from anti-inflammation to tissue regeneration [9,10]. Cavity filling is the essential demand for dental caries treatment, and preventing secondary caries is also expected, presenting new challenges to the materials applied in the oral cavity.

Resin, glass ionomer restorative materials, fluoride coating, and hydrogels have been widely used in dental caries. Among them, hydrogels have drawn the most attention due to their excellent biocompatibility, predictable degradation rate, tunable mechanical property, and good elasticity [11–16]. In addition, they can fill the defect sites and promote remineralization by simulating the extracellular matrix (ECM) and delivering various factors [17,18], antibiotics [19], and ingredients. Furthermore, the ECM-mimic hydrogel can pack the cells or growth factor to encourage tissue regeneration in the pulp [20,21]. These properties allow hydrogel to meet the specific requirements of dental treatment [22]. Other setbacks in caries care involve frequent encounters with the bacterial environment, consistent saliva flow, and oral cavity movement, emphasizing the significance of research and design of state-of-the-art functional hydrogels with antibacterial, injectable, and adherable capabilities [23]. To date, much research about hydrogels participating in dental caries management has been reported.

Herein, we present a summary of the functional hydrogels in treating dental caries in this paper (Fig. 1). According to the occurrence and development of disease, we begin with the reason and development of dental caries. Then we categorize the hydrogel-based strategies in treating dental caries with antibacterial or (and) remineralization capabilities. Next, the hydrogel-based dental pulp regeneration is summarized. Finally, we summarize this area and look at challenges of the present and the direction of the future.

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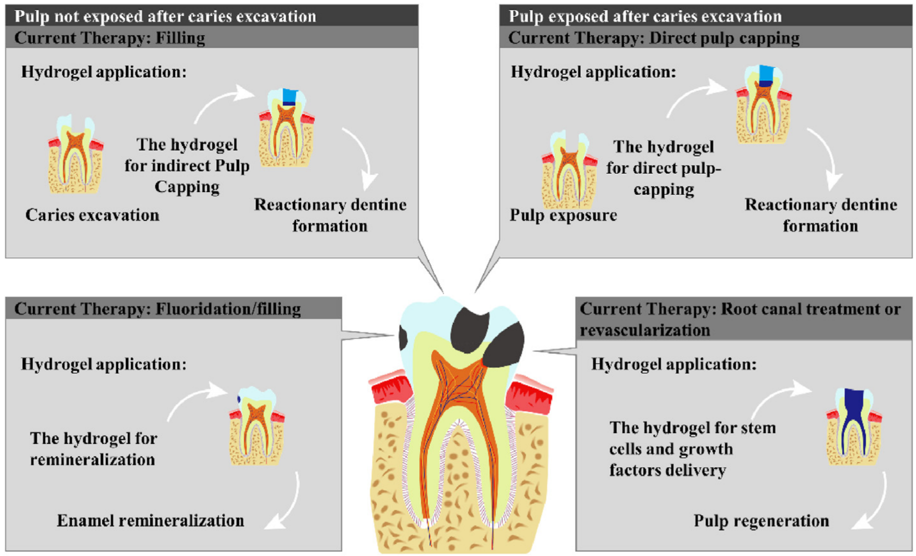

Fig. 1. The illustration of the hydrogel applications in dental caries.

2. The occurrence and development of dental caries

Dental caries is the disease involving bacterial infections that induces the destruction of local dental hard acellular tissue, and has become one of the most prevalent healthy problems worldwide [24]. Based on the development of caries, it can be divided into three major types, i) superficial caries, caries only infects the superficial enamel; ii) medium caries, caries impacts the enamel and partial dentin; iii) deep caries, the caries lesion effects the deep detin and even affects the pulp. According to the different stages of dental caries, various corresponding treatments are needed. To treat the superficial and medium caries, we only need to remove the caries tissues and then fill the resultant cavity. However, the lesion may be deep enough to affect the dental pulp, resulting in an inflammation state of the unsound pulp. When the disease progresses further, the pulp' vitality becomes non-recoverable, and the pulp may even need to be removed.

According to the current mainstream view, the acid generated from the bacterial fermentation of dietary carbohydrates is the direct reason for enamel demineralization, which initiates the progression of caries. Hence, bacterial control is the key to dealing with dental caries. The microbial communities that cause dental caries are varied, including streptococcus mutants (S. mutans), actinobacillus, lactobacillus et al. Among them, the *S. mutans* is primarily associated. Departing the pathogenic bacteria control, another critical aspect of preventing caries is inhibiting demineralization and promoting remineralization. The anti-caries effect of fluoride has been proven widely, which can hinder demineralization and promote lesion remineralization. Overusing fluoride leads to mottled enamel and even fluorosis, which may greatly threaten health [25]. To conquer the limitation of fluorosis and staining caused by fluoride overused, many agents were developed to trigger biomimetic mineralization, such as amelogenin-derived peptides [26,27], dentin phosphoprotein-derived peptides [28], peptides with beta-sheet structures [29], self-assembling peptide-amphiphiles [30], some inorganic materials [31,32] et al. Although many biomaterials are already available for those agents' delivery, a practical strategy is highly desired. Considering the moist environment in the oral cavity, the hydrogenous scaffold-hydrogel is suitable for application in this condition. As caries progresses, the pulp activity is irreducibly affected, requiring root canal treatment or pulp regeneration. To realize the regeneration of pulp tissue, some biocompatible hydrogels can be employed that deliver the stem cells, growth factors, and other components.

3. Hydrogels application in dental caries

According to the process of dental caries, antibacterial and remineralization are critical points in the non-operative therapy of dental caries. Generally, the non-surgical treatment of caries is treated with medication, penetrating resin, or remineralization methods without using dental drills or other instruments for cavity preparation. To date, hydrogel applications involve tooth fluoride, cavity filling, and caries needing root canal treatment. The summary of hydrogel applications in dental caries treatment with antibacterial and (or) remineralization capabilities is listed as follows.

3.1. Antibacterial

As the leading threatening microorganism of oral dental caries, the *S. mutans* can synthesize exopolysaccharides (EPS) via glucosyltransferases (Gtfs), stimulating biofilm formation, which is a stable shelter for bacterial proliferation. Prolonging the contact time with the treatment site would increase the chance to realize bacterial control. Many traditional agents possessing antibacterial ability, especially the silver, have been used in dental settings for a long history. With a substantial antibiotic effect against bacteria (no matter Gram negative or positive) [33], silver and mercury amalgam have been used with great success for dental filling over one century [34], which can continuously prevent secondary caries. However, they gradually fell into disuse due to the potential toxicity and unfavored staining [35]. As another form of silver doped material, silver diamine fluoride (SDF) is a kind of liquid for application to carious lesion, with or without cavities. It can serve as an efficacious agent that has the potential to reduce the number of bacteria and stop the development of dental caries [36]. The brown staining and threat to healthy dental tissues and skin compromised its use, as the uncontrolled release hinders the safety delivery. To realize controlled release, such biomaterials as polyvinyl alcohol (PVA) [37,38], alginate [39], and carboxymethyl cellulose (CMC) [40] have already been utilized to load silver, which can swell to form hydrogels in aqueous settings. Also, silver cross-linked nanocrystalline cellulose (CNC) has shown the controlled release formula of silver to prolong the antimicrobial activity in dental practice [41]. Apart from silver-based biomaterials, as a kind of linear cationic biopolymer with good biological compatibility, chitosan (CS) exhibits good adhesion property to mucosal surfaces. CS gel combined with Zinc oxide NPs (ZnO-NPs) doped Ze (ZnONC) has obtained a synergistic effect for better antibacterial, showing good biocompatibility *in vitro*.

Apart from the inorganic metal ions-relative strategies, the organic-based molecules have shown remarkable developments recently, among which the antimicrobial peptides (AMPs) have gained great attraction as a viable biomolecular alternative owing to their superior anti-bactericidal properties and broad-spectrum activity. (Fig. 2). As natural components of the innate immune response, AMPs own huge potential in dental applications with no risk of developing drug-resistant bacteria, which is the most criticized area of antibiotic abuse. What's more, compared with antibiotics, AMPs have higher stability and do not require special storage conditions [42]. Nowadays, AMPs are applied in dental applications for implants-coating [42] and adhesive materials doping [43,44] to combat pathogens [45]. Many researchers have explored different conjugation strategies to reduce the toxicity risk. Kumar et al. [46] demonstrated a kind of functional AMP based aurein 2.2. The hyperbranched polyglycerol (HPG)- modified AMPs showed substantially better than that of the available polymer−AMP conjugates activities. Benefiting from the protection of HPG, the modified AMPs exhibited excellent biocompatibility, effective MICs, and proteolytic stability, which improved their application *in vivo* potentially. Also, by conjugating cell-penetrating peptides with AMPs, the chimeric peptides could achieve the goals of cell-penetrating and antimicrobial, and the positive biocompatibility was determined by the *in vitro* and *in vivo* experiments [47].

In addition, due to the multi-microbiota environment in the oral cavity, new preventive strategies based on manipulating oral microbiota have been developed recently. Among the candidate bacteria, the *Lactobacillus* is the ideal choice, as it can exhibit excellent activity against oral cavity pathogens [48,49]. After biofilm formation by the applied *Lactobacillus,* the *S. mutants* adhesion to tooth or hydroxyapatite discs can be interfered. The *L.paracasei* 28.4 also shows inhibitory effects on *S. mutans*. However, its application was limited by hard storage and short-term live. To address this, the gelatin hydrogel can be used to capsule living *L. paracasei 28.4* to achieve enhanced *S. mutans*. Inhibition [50].

Apart from directly killing or inhibiting bacteria, the hydrogel from zwitterionic polymer can resist the adhesion of cariogenic bacteria to prevent bacterial proliferation on the enamel [52], which holds enormous clinical potential in effectively stopping the caries-causing process and protecting against dental caries (Fig. 3). What's more, to conquer the shield from extracellular polymeric substances (EPS), Dong, etc., validated that the cationic dextran could effectively destroy the biofilm of the surface of the tooth, owing to the induced phase transition of EPS, which may be selected as promising generic clinical reagents in oral infection control [53]. Taking advantage of the high bactericidal efficiency, and noninvasive nature, antimicrobial photodynamic therapy (aPDT) has gained much attention for oral and dental application [54]. Du etc., taken

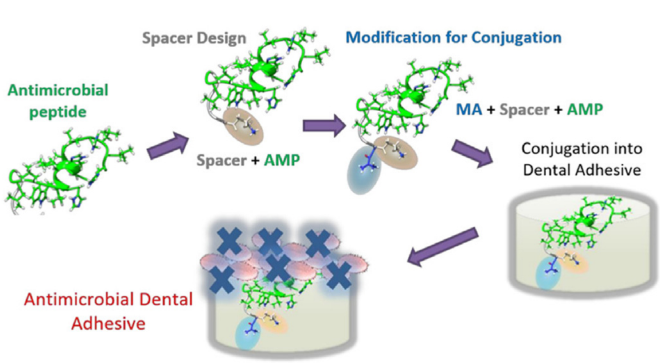

Fig. 2. The antimicrobial peptides (AMPs) application in the hydrogel to antibacterial. The figure was adapted with permission from Ref. [51]. Copyright 2020 American Chemical Society.

chlorin e6 (Ce6) as a photosensitizer to inhibit the cariogenic bacteria and the progression of Early childhood caries *in vitro* and *in vivo*, providing a new novel approach for daily oral hygiene [55].

3.2. Remineralization

When dental caries appears, the common strategy is to fill the cavity after removing the decayed material. However, the clinical filling material is kind of a polymer with no bioactivity, which may lead to secondary caries. Remineralization of superficial dental structures by non-invasive therapeutic procedures has been receiving more and more attention in recent decades and its medicinal value has been generally recognized. With the high adhesive property of hydrogel, it's reasonable to combine it with the ingredient possessing remineralization capability.

The enamel is a highly mineralized material composed of highly organized hydroxyapatite nanocrystals. To achieve the remineralization of enamel, versatile approaches are developed, including replenishment of mineral ions (i.e., calcium, phosphate, and fluoride) from dental varnishes; filling composites, glass ionomers, toothpaste, dentifrice, or mouth rinse solutions; and depositing fluorapatite (FAP)-like phases within the enamel [57]. However, the therapeutic effects of these approaches are unsatisfactory due to the limited contact time with the tooth. The hydrogel can load the remineralization-promoted agents and prolong the contact time. Ning et al. showed that the agarose gel holding 0.26 M Na_2HPO_4 and $CaCl_2$ could deposit hydroxyapatite crystals onto the dentin surface, providing an easy way to achieve dentin remineralization [58].

As the most enriched extracellular matrix protein of enamel, amelogenin is thought to serve an important role in the formation of enamel crystals and enamelin-derived peptides in stratified tissues, both of which are the keys to the restoration of dental caries. After being cultured with amelogenin-loaded hydrogel, microhardness of the enamel's surface was significantly increased. Also, the entire length of amelogenin exhibited inhibition properties towards biofilm composed of *S. mutans* and *S. sanguinis*, though the underlying mechanism is unclear. In addition, amelogenin displayed good biocompatibility when cultured with gingival fibroblast. Xu et al. found that the amelogenin released from hydrogel could increase the remineralized enamel's microhardness [59]. The chitosan hydrogel loaded with abundant amelogenin could promote faster mineral induction and result in organized crystal growth of hydroxyapatite [60]. Apart from the entire length of amelogenin, the derived peptide, like QP5 et al. also could act as the remineralization elements in the buffer [61].

The injectable hydrogel can transfer from liquid to solid at the target site after injection, allowing it to quickly fill the irregular cavity shape and mimic the natural extracellular matrix. The hydrogel prepared by a premixture of maleic chitosan, thiolated alginate, b-glycerophosphate calcium phosphate, and calcium carbonate showed excellent mineralization with highly crystallized Hap properties [62]. Zhao et al. took polyvinyl alcohol loading enamel analog as artificial tooth enamel, exhibiting high rigidity, stiffness, intensity, viscoelasticity, and toughness that exceeded the properties of enamel and previously fabricated bulk enamel-inspired materials. (Fig. 4) [31].

3.2.1. Anti-bacterial together with remineralization

With the dynamic course of dental caries, it is hypothesized that the integrated action of bacterial inhibition and remineralization has the ability to stop the development of caries. Hydrogels containing chitosan may inhibit bacterial growth because their protonated positive charge can interact with bacterial cell walls, leading to bacterial aggregation and death, resulting in a direct or indirect reduction in biofilm biomass, lactate production, and metabolic activity. The hydrogel can dope with silver or some antimicrobial peptides, as the non-antibiotics strategy can avoid antibiotics-induced dysbacteriosis in the oral cavity (Fig. 5). To achieve the remineralization of enamel or dentin, the categories can be roughly divided into two kinds. i) using polymer film to finish the surface

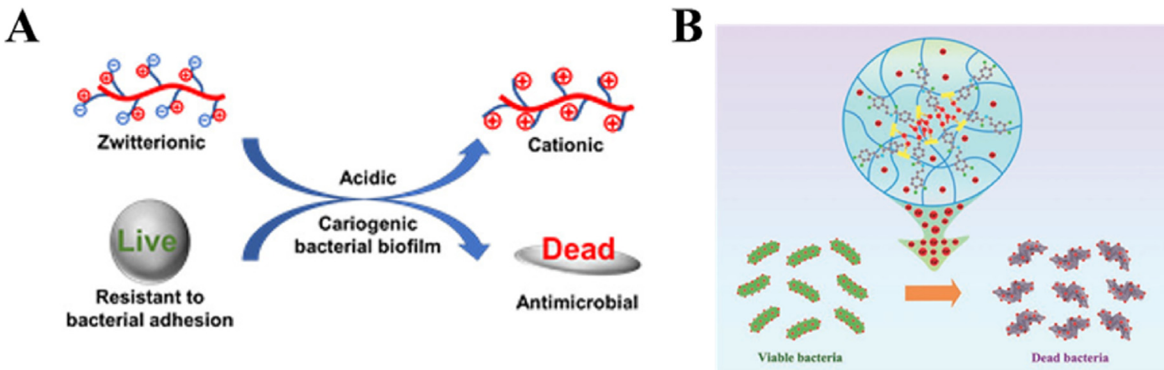

Fig. 3. The two different ways of hydrogel to anti-biofilm. The images were reprinted with permission from Refs. [52,56].

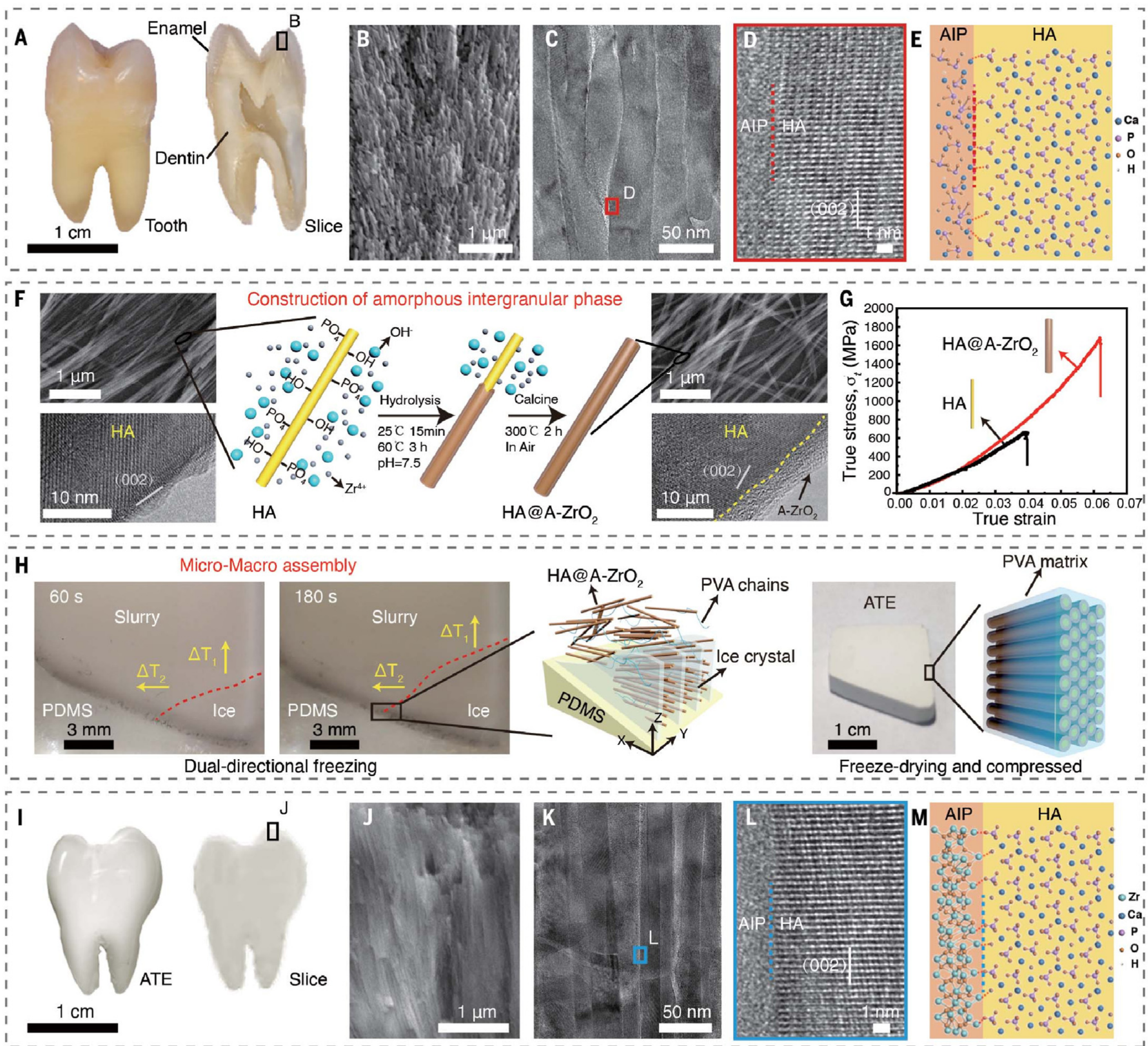

Fig. 4. The multiscale engineered artificial tooth enamel in the hydrogel. The images were reprinted with permission from Ref. [31].

with poly (amidoamine) [63], phase-transited lysozyme/C-terminals of the amelogenin peptide [64], and lysozyme conjugated with poly (ethylene glycol) [65]; ii) utilizing the polymer additives to simulate the role of NCPs, such as casein phosphopeptide (CPP) [66,67], polyaspartic acid (PASP) [68,69], and polyacrylate acid (PAA) [70,71] and so on. Considering the constant acid secretion by bacteria within the biofilm, the loss of tooth minerals will continue with the repeated dissolution of minerals [72]. So, the antibiofilm activity is of great significance in dental remineralization. He et al. developed a dual-functional nanocomposite by uniting the zwitterionic poly (carboxybetaine acrylamide) and amorphous calcium phosphate, which significantly inhibited the adhesion and biofilm formation of *Streptococcus mutans (S. mutans)* and the remineralization of demineralized enamel was also achieved [52]. Taken advantage of the antibacterial of zwitterionic polymers and the

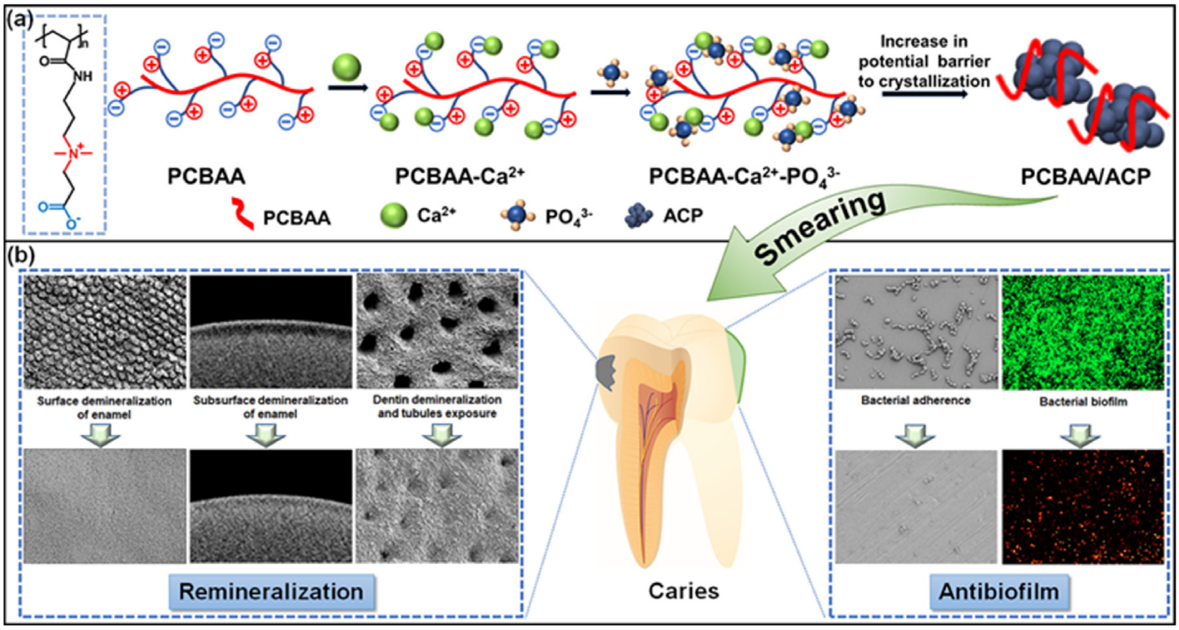

Fig. 5. A strategy to relegalized Remineralization and Antibiofilm Functions with Polyzwitterion Manipulates. The images were reprinted with permission from Ref. [52].

remineralization of amorphous calcium phosphate, this dual-functional structure with anti-biofilm and remineralization properties held great clinical potential.

4. Hydrogels application in root canal treatment

Clinically, when dental caries progresses without appropriate intervention, the pulp tissues located within the tooth can be severely inflamed, and induce inflammation [73]. Root canal surgery is usually performed to remove necrotic tooth tissue [74], along with the removal of blood vessels and nerves. As a result, the tooth become devitalized and prone to postoperative fractures [75]. Consequently, there is an urgent need for an alternative to conventional root canal treatment. Recently, the tissue engineering strategy has shown as a progressive approach to restore the damaged dental structures and replace its biological capabilities by co-delivery the scaffolds and stem cells [17,76] (Fig. 6). Direct pulp capping surgery involves the application of biologically active material (like calcium hydroxide and mineral trioxide aggregate) to the exposed area. Still, the uncertain direction of development does not guarantee the outcome of the treatment [77]. Regenerative endodontic treatment includes several strategies to rejuvenate the pulp through biologically based methods. Evoked bleeding techniques have regenerated pulp-like tissue within sterilized root canals. Through the above approach gain some accomplishment, the tedious operation places high demands on the operator in the clinic. Intending to promote de novo dentin and pulp regeneration, pulp-dentine tissue engineering aims to restore and repair tissues in situ of the tooth with the improved outcomes of direct pulp capping and regenerative endodontic treatment. To conquer the problem that the insufficient blood supply may induce high mortality in pulp regeneration, angiogenic growth factors can be

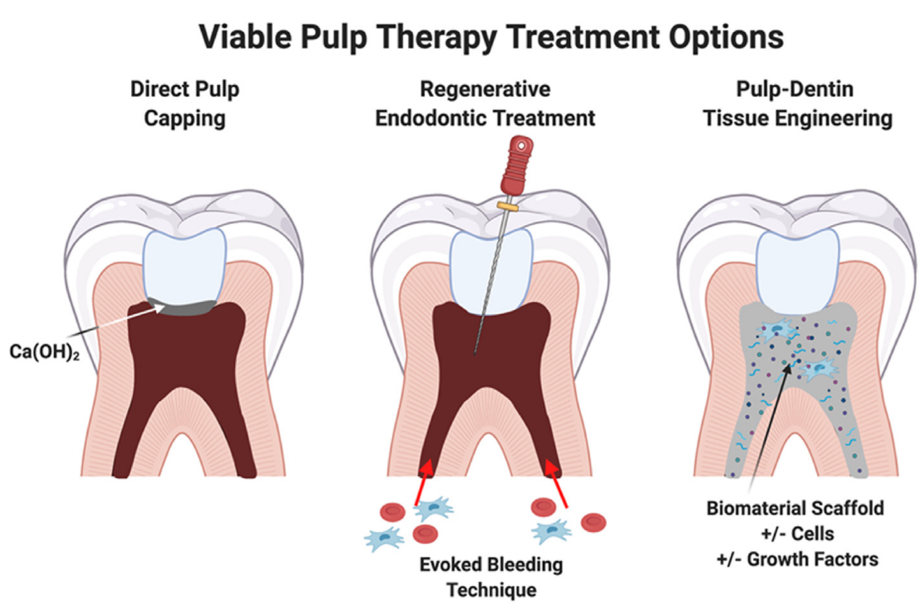

Fig. 6. A simple regenerative endodontics strategy from hydrogel delivery with cells and growth factors. The images were reprinted with permission from Ref. [91].

delivered synchronously to enhance revascularization. Liu etc., took heparin-conjugated gelatin nanospheres to deliver vascular endothelial growth factor (VEGF), which could efficiently accommodate dental pulp stem cells (DPSCs) and support the growth and pulp tissue development *in vivo* [78]. Also, the cells loaded with hydrogel microfiber achieve the non-factor vascularized dental pulp regeneration with DPSCs and human umbilical vein endothelial cells (HUVECs) co-delivery [79]. The incompact three-dimensional structure from aggregated microfibers could provide the convenience for substance exchange between stem cells and others, enhancing cell adhesion, growth, proliferation, and differentiation in applying the stem cells in pulp regeneration. In addition, as the entire length of the human tooth root canal is up to 11–13 mm, the current root canal filling materials usually require specialized equipment to fill the root canal compactly, which may impact the patient's comfort. Hence, if the hydrogel can be injectable, it will be promising in root canal treatment applications. As a hydrogel with excellent injectability, biocompatibility, and biodegradability, gelatin methacryloyl (GelMA) has been reported for mass studies in tissue engineering [80,81]. GelMA has several valuable characteristics for biological applications, including hydrophilicity, integrin-binding motifs, and matrix metalloproteinase (MMP) degradation [82,83]. Many infections are associated with upregulated levels of MMPs in the periapical area during periapical pathology development [84]. Hence, the GelMA can act as a scaffold to deliver factors into the root canal to achieve gradual release after application. To conquer the uncontrollably released profile of chlorhexidine (CHX, a usual antibacterial agent in dental practice), Ribeiro et al. developed GelMA hydrogel system loaded with CHX for intraoral delivery of CHX as a suitable ablation strategy for dental infections [85]. The outcomes show that the GelMA-based injection-ready drug delivery system is ideal for endodontic and periodontal applications. Also, the chitosan base [86–88], and Alg-based hydrogel [89,90], can act as a delivery system to deal with pulp disease.

5. Challenges in dental caries treatment through hydrogel

Despite hydrogel having shown great application potential in dealing with dental caries, many restrictions also need to be conquered. The most crucial property is swelling that induces the risk of abscission. The swelling of hydrogel is derived from the interaction between hydrophilic polymers and water molecules [92,93]. To reduce the swelling ratio of hydrogel, the double-network hydrogel has been developed to increase the cross-link density [94,95]. In addition, nanomaterials, nano-micelle, and hydrophobic polymer chains can also regulate the swelling property [96]. Also, some studies took the intrinsic accumulation of metal ions (like Cu) to reduce the swelling and enhance the hydrogel's electron and antibacterial properties [56].

Another drawback of hydrogel application in the oral cavity is insufficient adhesion due to the continuous saliva flow. Many attempts have been made to increase the adhesion ability, but the results are unsatisfactory. In the skin wound, many strategies can be used, such as direct adhesion [97], EDC/NHS [98], pH tuning [99], UV irradiation [100], temperature tuning [101], and voltage [102], as many active groups can be exposed. However, with a high mineralization level, the enamel has almost no group for chemical adhesion. Inspired by the artful strategy from the wild, mussel-inspired systems have been developed for high adhesion [103]. Benefit from the catechol side chains of L-3, 4-dihydroxyphenylalanine (L-DOPA) derived from folded mussel foot protein (Mfp), the mussels can strongly attach to almost all inorganic and organic surfaces in an aqueous environment, which is similar to the moist environment of the mouth [104,105]. Taken together, the mussel-inspired hydrogel may have huge application prospects in dental caries and other oral disease treatments.

6. Conclusion and outlook

As a biopolymer with unique characteristics and a wide range of applications in biomedicine, the hydrogel has been under multiple investigations. However, several issues are still anticipated for further research. Many studies so far have demonstrated that hydrogel with suitable ingredient encapsulation can increase the antibacterial and remineralization of the tooth, showing excellent application potential in the treatment of dental caries. Nowadays, the hydrogel is widely serviceable in restorative dentistry for dental caries and pulp tissue regeneration. In the future, the hydrogel may be utilized for the treatment of versatile diseases in the field of dentistry. It is essential to highlight the crucial role of hydrogel in combination with natural biomolecules and drugs in pulp regeneration and other tissue engineering.

Despite the successful and encouraging research of these hydrogel-based materials in dental caries treatments, challenges remain in designing and preparing the materials and achieving the ultimate aim, dentin restoration. With this regard, attentions and efforts could be concentrated on the following aspects. Firstly, the adhesion property should be enhanced under moist conditions. The oral cavity is a naturally moist and warm environment, ensured by the continuous saliva flow, demanding the higher adhesive ability of hydrogel. Considering the speech, drinking, and swallowing, the applications of hydrogel on the tooth surface need stronger adhesion. The second point focuses on releasing the ingredients that doped in the hydrogel. The tooth is the most rigid tissue in the human body, which needs the element to be small or with active targeting to the lesion. The enamel and dentin are hard to penetrate, while the caries' position is high permeability. The design can focus on diversity between the tissue to achieve a better delivery result. Finally, the hydrogel with the ability to directly detect oral disease is highly expected. Currently, the means of dental detection are limited to the clinical experience judgment and X-ray. Hence, it's necessary to develop hydrogels with detection capacity. Although challenges remain, we hope the ongoing achievements in these fields will drive the revolution of both material and medical science as well as associated engineering technologies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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