Bioactive Synthetic Peptides for Oral Tissues Regeneration

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Regenerative therapy in oral tissues has gained relevance since tissue loss due to congenital or acquired diseases as well as trauma is a major health problem worldwide. Regeneration depends on the natural capacity of the body and the use of biomaterials and bioactive molecules that can module the processes to replace lost or damaged tissues and restore function. The combined use of scaffolds, cells, and bioactive molecules such as peptides is considered the best approach to achieve tissue regeneration. These peptides can induce diverse cellular processes as they can influence cell behavior and also can modify scaffold properties, giving as a result the enhancement of cell adhesion, proliferation, migration, differentiation, and biomineralization that are required given the complex nature of oral tissues. Specifically, synthetic peptides (SP) have a positive influence on scaffold biocompatibility since in many cases they can mimic the function of a natural peptide or a full-length protein. Besides, they are bioactive molecules easy to produce, process, and modify, and they can be prepared under well-defined and controlled conditions. This review aims to compile the most relevant information regarding advances in SP for dental and periodontal tissue regeneration, their biological effects, and their clinical implications. Even though most of the SP are still under investigation, some of them have been studied *in vitro* and *in vivo* with promising results that may lead to preclinical studies. Besides there are SP that have shown their efficacy in clinical trials such as P11-4 for enamel regeneration or caries prevention and ABM/P-15 for cementum, periodontal ligament (PDL), and alveolar bone on a previously calculus- and biofilm-contaminated zone. Also, some SP are commercially available such as PTH1-34 and PepGen P-15 which are used for bone defects treatment.

Keywords: synthetic peptide, oral tissue, periodontal regeneration, dental materials, bioactive peptides, dental regeneration

INTRODUCTION

A peptide can be defined as a short polymer of amino acids. Depending on the definition of different authors, sizes can vary from <20, <50, to <100 (Lien and Lowman, 2003; Sato et al., 2006; Vlieghe et al., 2010; Hamley, 2017). In the last decades, more than 7,000 native peptides (NP) with important human physiological functions have been studied (Fosgerau and Hoffmann, 2015) since they have

roles as cell adhesion motifs, structural peptides, cell-penetrating, and tumor-homing peptides, antimicrobial peptides, peptide hormones, growth factors, and matrix metalloprotease substrates, amyloid peptides, neuropeptides, peptide tags, and other miscellaneous NP (Hamley, 2017). However, NP are often not directly suitable for therapeutic use because they have intrinsic weaknesses, like poor chemical and physical stability, short circulating plasma half-life, low oral bioavailability, and rapid removal from the circulation by the liver and kidneys (Vlieghe et al., 2010; Fosgerau and Hoffmann, 2015; Erak et al., 2018; Lau and Dunn, 2018).

The use of peptides for human therapeutic began with peptides such as insulin and adrenocorticotrophic hormone (ACTH) isolated from natural sources in the first half of the 20th century (Banting et al., 1922). Further, with sequence elucidation and chemical synthesis of peptides in the 1950s, synthetic oxytocin and vasopressin entered to clinical use (Stürmer, 1989).

In recent years the pharmaceutical industry has increased attention to new therapeutic peptides, constantly reaching clinical application (Vlieghe et al., 2010; Dang and Süssmuth, 2017). By 2018 more than 60 peptides were approved by the FDA and more than 600 were in clinical and preclinical trials (Vlieghe et al., 2010; Erak et al., 2018). The production of therapeutic synthetic peptides (SP) has become possible with recent developments of solid-phase peptide synthesis (Vlieghe et al., 2010) and novel synthetic strategies allow the modulation of pharmacokinetic properties and target specificity through amino acid, backbone modification, incorporation of non-natural amino acids, and peptide conjugates (Conjugation to polyethylene glycol (PEG), lipids, and proteins such as Fc fragments) extending the half-life or improving solubility (Sato et al., 2006; Fosgerau and Hoffmann, 2015; Lau and Dunn, 2018).

Based on their chemistry, SP are categorized concerning their relationship to NP molecules: native, analog, and heterologous. A native has the same sequence as an NP product, analogs are defined as modified or substituted versions of NP with improved drug properties, and heterologous peptides were discovered independently of the natural peptide through synthetic library screening, phage display, or other methods (Sato et al., 2006; Vlieghe et al., 2010; Hamley, 2017; Lau and Dunn, 2018).

As potential therapeutics SP offer several advantages over other molecules: increased specificity, small size (increasing their potential to penetrate further into tissues) (Sato et al., 2006), excellent safety, tolerability, and efficacy profiles in humans (Fosgerau and Hoffmann, 2015). SP also have lower cost and production complexity compared with protein-based biopharmaceuticals (Fosgerau and Hoffmann, 2015). They are generally less immunogenic than recombinant proteins and antibodies, show higher activity per unit mass, and have greater stability (can be stored at room temperature for a long time). Additionally, degradation products of peptides are amino acids, and given their short half-life, few peptides accumulate in tissues, minimizing the risks of complications caused by their metabolites and the risks of systemic toxicity (Vlieghe et al., 2010).

Oral tissue regeneration is crucial since their congenital or acquired loss by trauma or diseases is a major health problem (Abou Neel et al., 2014). In this regard, the healing capacity of the body and the use of bioactive molecules able to module the processes to replace lost tissue and restore function are key. The best approach to achieve tissue regeneration is the combined use of scaffolds, cells, and bioactive molecules such as SP which can induce diverse cellular processes as they can influence cell behavior and also can modify scaffold properties. SP enhance cell adhesion, proliferation, migration, differentiation, and biomineralization that are required given the complex nature of oral tissues. Therefore, the purpose of this review is to discuss recently developed advances regarding SP for dental and periodontal tissue regeneration. Our goal is to highlight the current approaches in their applications to demonstrate their potential and at the same time to draw attention to the advances and the issues which need to be addressed for progressing in oral tissues enginnering.

DENTAL TISSUE REGENERATION

Dental caries remains the most common disease worldwide, and it is defined as pathophysiological processes in the dental biofilm that cause an imbalance in the demineralization-remineralization equilibrium, leading to a net loss of tooth minerals progressing to a cavity. This process begins by dissolution of the subsurface mineral tooth structure knowing like white spot, followed by progression to irreversible cavitation of the mineralized surface layer (Han et al., 2017; Jablonski-Momeni et al., 2019; Pandya and Diekwisch, 2019).

When a tooth is damaged by caries, the enamel and dentin are degraded by enzymes and acids from microorganisms. In this situation, the odontoblast layer in the pulp chamber releases bioactive molecules with reparative potential for dentinogenesis. However, the exact mechanism that regulates this process is unclear and dentin regeneration remains a great challenge in the clinic (Smith et al., 1995; Bleicher, 2014; Wang et al., 2014).

Additionally, after caries occur, the clinical intervention is focused on removing the infection, preserving as much natural tooth structure as possible to use adhesive restorative materials to replace the lost enamel and dentin. In the case of the pulp chamber exposition, the direct capping with calcium hydroxide ($CaOH_2$) and/or mineral trioxide aggregate (MTA) is the only clinical treatment option focused on the preservation of pulp vitality by the formation of reactionary dentin (tertiary dentin) (Huang, 2011; Hilton et al., 2013). Although these treatments have, in some cases, success rates (60–80%), nowadays, there is not an effective treatment in the clinical area to induce cellular repair of the enamel, dentin, and pulp. SP (**Figure 1**) have emerged as an alternative for the regeneration of dental organ tissues (**Table 1**).

Enamel

Dental enamel is a calcified tissue that forms the outer protective covering of the anatomical crown of a tooth and is produced by ameloblasts. However, these enamel-forming cells, as well as the enamel organ stem cells are lost at the time of tooth eruption.
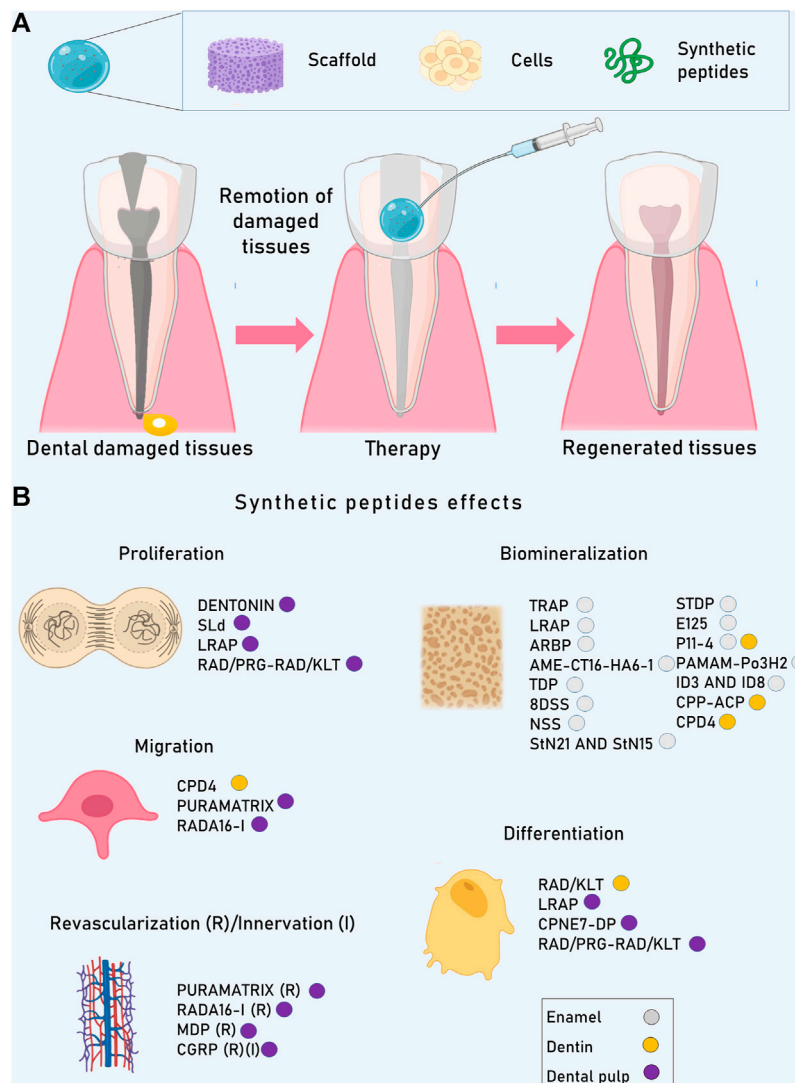
FIGURE 1 | The combined use of scaffolds, cells, and bioactive molecules such as SP is considered the best approach to achieve tissue regeneration. **(A)** Dental organs can be damaged principally by caries. Depending on the damage level, enamel, dentin or even pulp can be injured. Advances in the field of SP could be beneficial to treat and regenerate lost tissues. **(B)** SP can induce diverse cellular processes in dental tissues as they can influence cell behavior and also can modify scaffold properties, giving as a result the enhancement of cell proliferation, migration, revascularización, innervation, differentiation, and biomineralization.

Mature enamel is mainly composed of inorganic material (96%) formed by crystals of hydroxyapatite (HA) and a small proportion of water (3%) and proteins (1%) that bind the mineralized fibers together (Hara and Zero, 2010; Pandya and Diekwisch, 2019). Also, more than 40 trace elements have been identified in enamel, which can be incorporated in various ways: ion exchange in the hydration shell, which is the layer of water adjacent to the crystal; direct absorption on the surface of the crystal; and substitution with components of the crystal of similar size and charge. The acid solubility of a tooth and thus its caries resistance can be affected by the crystal size and shape, and the proximity of the crystals (Hara and Zero, 2010; Kind et al., 2017; González-Cabezas and Fernández, 2018; Dissanayake et al., 2020; Farooq and Bugshan, 2020).

Peptides Derived from the Amino Acid Sequence of Enamel and Dentin Proteins

Peptides derived from enamel and dentin proteins have been developed to prevent demineralization and/or promote the remineralization process (Chung and Huang, 2013; Yang et al., 2016; Buzalaf et al., 2017). For instance, amelogenin is an important protein involved in the growth and maturation of enamel crystals in the newly formed enamel matrix and is absent in mature enamel (Buzalaf et al., 2017; Farooq and Bugshan, 2020). This protein has been used to form chitosan-amelogenin hydrogel (CS-AMEL) to promotes enamel remineralization. As a result of proteolysis of amelogenin by matrix metalloproteinase 20 (MMP-20) during the biomimetic enamel regrowth, the newly

TABLE 1 | Synthetic peptides used for dental tissue regeneration.

ENAMEL			
Peptide	Methodology	Effect	References
Amelogenin peptide (TRAP)/(LRAP)	*In vitro* study with samples from bovine enamel and human molars. Artificial lesion: 30% phosphoric acid for 10 s. Remineralization: Artificial saliva for either 5 or 10 days at 37°C	Promotes enamel crystal nucleation and growth. Improves remineralization of enamel surface lesions	Han et al. (2017); Dissanayake et al. (2020); Farooq and Bugshan (2020); Wang et al. (2020)
Amelogenin repeat-based peptide consisting of 22-residues in five tandem amelogenin polyproline repeat (GLn-Pro-X) and a seven residues hydrophilic tail	*In vitro* study in bovine permanent incisors. Artificial lesions: 50 mM acetic acid (pH 4.5), 2.2 mM $Ca(NO_3)_2$, 2.2 mM KH_2PO_4, 5.0 mM NaN_3, and 0.5 ppm NaF; at 37°C for 3 days Remineralization: 12 days at 37°C pH cycling model. Remineralization solution: 20 mM HEPES (pH 7.0), 0.9 mM KH_2PO_4, 1.5 mM $CaCl_2$, 130 mM KCl, 1.0 mM NaN_3 for 22 h *In vivo* study in rat caries model using the sprague-dawley rat model of early enamel lesions induced by *S. mutans*	Promotes the remineralization of enamel caries. Bind on the enamel surface, can stabilize amorphous calcium phosphate (ACP), it can control the crystallization of hydroxyapatite (HA)	Lv et al. (2015); Han et al. (2017); Kind et al. (2017); Mukherjee et al. (2019); Ding et al. (2020)
Ame-CT16-HA6-1 (16 carboxyl-terminal residues of amelogenin join to a sequence of SVSVG-MKSPRR denominated HA6-1)	*In vitro* study in human un-erupted third molars Artificial lesions: 37% phosphoric acid for 30 s Remineralization: Simulated saliva (1.5 mM Ca^{2+}, 0.9 mM HPO_4, and HEPES) for 7 days	In combination with carboxymethyl chitosan and ACP, form enamel-like apatite crystals and bind to demineralized enamel specifically	Chung and Huang (2013); Chung and Li (2013); Kind et al. (2017); Xiao et al. (2017); Ding et al. (2020)
Tuftelin derived peptide (TDP)	*In vitro* study in human third molars Artificial lesions: 50 mM acetic acid (pH 4.5), 2.2 mM $Ca(NO_3)_2$, 2.2 mM KH_2PO_4, 5.0 mM NaN_3, and 0.5 ppm NaF at 37°C for 3 days Remineralization: 12 days pH cycling model remineralization solution: 20 mM HEPES (pH 7.0), 0.9 mM KH_2PO_4, 1.5 mM $CaCl_2$, 130 mM KCl, and 1.0 mM NaN_3 for 22 h	Nucleation of HA crystals and promotion of remineralization of initial carious lesions	Chung and Huang (2013); Chung and Li (2013); Kind et al. (2017); Xiao et al. (2017); Ding et al. (2020)
DPP-derived peptide: (8DSS)	*In vitro* study in bovine permanent incisors. Artificial lesions: 50 mM acetic acid (pH 4.5), 2.2 mM $Ca(NO_3)_2$, 2.2 mM KH_2PO_4, 5.0 mM NaN_3 and 0.5 ppm NaF at 37°C for 3 days and low-speed magnetic stirring (100 rpm). Remineralization: 12 days of pH cycling model remineralization solution: 20 mM HEPES (pH 7.0), 1.5 mM $CaCl_2$, 0.9 mM KH_2PO_4, 130 mM KCl, 1.0 mM NaN_3 for 23 h *In vivo* study in rat caries model using the sprague-dawley rat model of early enamel lesions induced by *S. mutans*	Promotes the uniform deposition of nanocrystalline calcium phosphate over demineralized enamel. Nucleates the formation of HA and inhibit demineralization	Hsu et al. (2011); Chung and Huang (2013); Chung and Li (2013); Yang et al. (2014); Yang et al. (2016); Alkilzy et al. (2018a); Ding et al. (2020)
NSS peptide (an aspartate is replaced for asparagine from DSS sequence of DPP)	*In vitro* study in human third molars Artificial lesions: 1M citric acid (pH 2) for 2 min. Remineralization: Artificial saliva (6.84 mM NaCl, 5.37 mM KCl, 5.44 mM $CaCl_2$-$2H_2O$, 4.42 mM NaH_2PO_4-$2H_2O$, 0.21 mM Na_2S-$9H_2O$ and 16.65 mM urea) at 37°C for 14 days	Promotes HA crystals formation onto the enamel surface	Chung and Huang (2013); Chung and Li (2013); Kind et al. (2017); Xiao et al. (2017); Ding et al. (2020)
StN21 and StN15	*In vitro* study in porous HA blocks Artificial lesions: 0.1 M acetic acid at pH 4 for 120 h. Modified buffer (100 mM NaCl, 40 mM KCl, 4.3 mM Na_2HPO_4, and 1.4 mM KH_2PO_4) pH 7.39 for 120 h	Bind to HA and have a protective effect on HA against acid attack	Buzalaf et al. (2017); Valente et al. (2018); Arifa et al. (2019)
Statherin-derived peptide (DpSpSEEKC)	*In vitro* study in human premolars Artificial lesions: 37% phosphoric acid for 45 s. Remineralization: Artificial saliva (1.5 mM $CaCl_2$, 0.9 mM KH_2PO_4, 130 mM KCl, 1 mM NaN_3, and 20 mM HEPES) at 37°C for 12 h	Acts as a nucleation template	Yang et al. (2017)

TABLE 1 | (*Continued*) Synthetic peptides used for dental tissue regeneration.

ENAMEL			
Peptide	**Methodology**	**Effect**	**References**
Elastin-like polypeptide (E125)	*In vitro* study in bovine enamel Artificial lesions: 37% phosphoric acid for 1 min. Remineralization: Simulated oral fluid (137.35 mM NaCl, 4.17 mM NaHCO3, 3.01mM KCl, 7.17 mM K2HPO4•3H2O, 1.53 mM MgCl2•6H2O, 20 mM HCl, 0.90 mM CaCl2, 0.51 mM Na2SO4 and tris) at 37°C for 12 h, pH 7.3	Stabilizes ACP and induces the oriented crystal growth along the original enamel apatite nanocrystals, inducing the regeneration of enamel apatite crystal structure	Lv et al. (2015); Han et al. (2017); Zhou et al. (2018)
P11-4 (N-terminally acetylated, C-terminal amidated 11 amino acid residue peptide)	*In vitro* study in human third molars. Artificial lesions: 2.2 mM CaCl$_2$, 2.2 mM NaH$_2$PO$_4$, 50 mM acetic acid; pH 4.4 for 3 days at 37°C. Remineralization: Buffer 2 mM Ca(NO$_3$)$_2$, 1.2 mM KHPO$_4$, and 60 mM Tris/HCl (pH 7.4) for 14 days *In vivo* study, clinical application first an uncontrolled safety trial. Then randomized controlled trial (RCT) single-blinded study. 35% phosphoric acid and application of the peptide P11-4 and waiting for 3–5 min	Induces the precipitation of HA to attract Ca2+ ions, regenerate early carious lesions (white spot lesions)	Alkilzy et al. (2018a); González-Cabezas and Fernández (2018); Arifa et al. (2019); Jablonski-Momeni et al. (2019); Üstün and Aktören (2019); Kamal et al. (2020); Li et al. (2020)
The fourth-generation polyamidoamine dendrimer (PAMAM-Po3H2)	*In vitro* study in human third molars Artificial lesions: 37% phosphoric acid. Remineralization: Artificial saliva (1.5 mmol CaCl$_2$, 0.9 mmol K$_2$HPO$_4$, 130 mmol KCl, 1 mmol NaN$_3$ and 20 mmol HEPES) pH 7	Induces crystal remineralization with the same structure, orientation, and mineral phase of the intact enamel in a relatively short time	Brunton et al. (2013); Kind et al. (2017); Alkilzy et al. (2018b); Arifa et al. (2019); Pandya and Diekwisch (2019); Üstün and Aktören (2019); Bröseler et al. (2020); Dissanayake et al. (2020); Farooq and Bugshan (2020); Wang et al. (2020)
ID4 and ID8 peptides self-assembly	*In vitro* study in bovine permanent incisors Artificial lesions: 50 mM acetic acid (pH 4.5), 2.2 mM Ca(NO$_3$)$_2$, 2.2 mM KH$_2$PO$_4$, 5.0 mM NaN$_3$ and 0.5 ppm NaF at 37°C for 3 days and low-speed magnetic stirring (100 rpm). Remineralization: Artificial saliva (1.5 mmol CaCl$_2$, 0.9 mmol K$_2$HPO$_4$, 130 mmol KCl, 1 mmol NaN$_3$ and 20 mmol HEPES) pH 7	In combination with hydrogels could serve as the template to induce HA nucleation and promote biomimetic remineralization	Brunton et al. (2013); Kind et al. (2017); Alkilzy et al. (2018b); Arifa et al. (2019); Pandya and Diekwisch (2019); Üstün and Aktören (2019); Bröseler et al. (2020); Dissanayake et al. (2020); Farooq and Bugshan (2020); Wang et al. (2020)

DENTIN			
Peptide	**Methodology**	**Effect**	**References**
CPP-ACP Random from casein digestion	*In vivo/In vitro* studies in extracted intact human third molar teeth. After demineralization, the samples were cover with CPP-ACP and incubated in artificial saliva	Prevention of demineralization and enhancement of remineralization of enamel and dentin lesions. The enhancement of the bond strength at the resin/dentin interface during the restorative intervention	Rahiotis and Vougiouklakis (2007); Cao et al. (2013); Sattabanasuk et al. (2014)
P11-4 CH$_3$COQQRFEWEFEQQNH$_2$	*In vitro* study, extracted non-carious human third molars were used to create an artificial carious lesion and treated with the P11-4 peptide	To form hydroxyapatite crystals from supersaturated solutions/remineralization of caries lesions	Koch et al. (2018); de Sousa et al. (2019)
RAD/KLT peptide KLTWQELYQLKYKGI	*In vitro* studies to evaluate cell adhesion, viability, proliferation, morphology on hydrogel scaffolds, and odontogenic differentiation of hDPSCs. Also the proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs) cultured with hDPSCs/SAP-conditioned medium *In vivo* study in a rat partially pulpotomized molar model to evaluate the inductive role of the RAD/KLT peptides over rDPSC to induce tissue regeneration after 28 days	Induce odontoblastic differentiation from dental pulp stem cells, and achieve dentin regeneration *in vivo*	D'Andrea et al. (2005); Xia et al. (2020)

TABLE 1 | (*Continued*) Synthetic peptides used for dental tissue regeneration.

DENTIN			
Peptide	**Methodology**	**Effect**	**References**
CPD4 VNPKYKQKRR	*In vitro* studies with dental pulp stem cells (DPSCs) from human deciduous teeth. After osteogenic differentiation under peptides and proteins treatment, a Western blot (RUNX2, Smad1/5/8, and pSmad1/5/8, Col1, OCN, OPN, ALP, TAZ, and GAPDH) immunofluorescence (OCN, DAPI) and histological staining (ALP) were performed	Cell penetration activity and regenerate mineralized tissues like bone and dentin	Creutz et al. (1998); Choung et al. (2016); Seo et al. (2017); Lee et al. (2019)
	In vivo, mouse calvarial defect model with defect size of 5 mm, they used 25 animals in five groups as follows: 1) defect, 2) non-treated (NT)/collagen, 3) CDP4/collagen, 4) CPNE7/collagen, and 5) BMP-2/collagen		
Dentonin TDLQERGDNDISPFSGDGQPFKD	*In vivo* study where agarose beads, either soaked with dentonin or unloaded, were implanted into the pulps of half-moon-shaped class V cavities on the mesial aspect of the first maxillary rat molars and examined 8, 15, and 30 days after treatment	Enhances dental pulp stem cell proliferation and promotes the regeneration of damaged dentin	Liu et al. (2004); Nagel et al. (2004); Six et al. (2007)

PULP			
Peptide	**Methodology**	**Effect**	**References**
SLd (TDLQERGDNDISPFSGDGQPFKD)	*In vitro* cytocompatibility and proliferation assays with mouse 3T3 fibroblasts, and a test for proliferation and efficacy with DSPCs and alizarin red staining were performed	Enhances dental pulp stem cell proliferation	Nguyen et al. (2018)
	In vivo test for biodegradation: Subcutaneous dorsal implantation in female wistar rats and histological staining		
Leucine-Rich Amelogenin Peptide (LRAP)	*In vitro* analyses included the effects of the addition of the recombinant proteins or peptides on cell proliferation, differentiation, and adhesion of postnatal human dental pulp cells (DPCs)	Proliferation and differentiation of dental pulp cells	Huang et al. (2012)
	In vivo analyses were completed following the insertion of agarose beads containing LRAP or LRAP 8, 9 into exposed cavity preparations of rat molars. After 8, 15, or 30 days' exposure, the pulp tissues were analyzed for changes in histomorphometry and cell proliferation by PCNA staining		
Copine 7 derived peptide (Cpne7-DP) (KYKQKRRSYK)	Human dental pulp cells (HDPCs) and a mouse pre-odontoblast cell line, MDPC-23, were chosen for *in vitro* studies to characterize lineage-specific cell responses after Cpne7-DP treatment	Promotes dentin regeneration, differentiation cellular	Lee et al. (2020)
	In vivo Cpne7-DP was tested using a beagle dog model by generating dentinal defects of various degrees. Overall mineralization capacity of Cpne7-DP was tested *ex vivo*		
PuraMatrix™ (RAD Ac-(RADA)4-NH2)	The peptide hydrogel PuraMatrix™ was used as a scaffold system to investigate the role of dental pulp stem cells (DPSCs) in triggering angiogenesis and the potential for regenerating vascularized pulp *in vivo*. Human umbilical vein endothelial cells (HUVECs), DPSCs, or co-cultures of both cell types were encapsulated in three-dimensional PuraMatrix™ in a SCID mouse model for subcutaneous transplantation of human tooth root fragments loaded with cell/PuraMatrix™ constructs	Enables cell survival, cell migration, and capillary network formation in the absence of exogenous growth factors. Besides, DPSCs increases early vascular network formation and increases VEGF expression	Dissanayaka et al. (2015)

TABLE 1 | (Continued) Synthetic peptides used for dental tissue regeneration.

PULP			
Peptide	**Methodology**	**Effect**	**References**
Peptide hydrogel RADA16-I (COCH₃-RADARADARADARADA-CONH₂)	The β-sheet and grid structure were observed by circular dichroism, SEM, and AFM. Living cell staining, proliferation, cytoskeleton in DPSCs. Migration assay in DPSCs and HUEVECs. Western blot	Self-assembly, microenvironment-simulating extracellular matrix, therapeutic delivery	Fermini et al. (2018); Mu et al. (2020)
RAD/PRG – RAD/KLT (RAD Ac-(RADA)4-NH2) (PRG Ac (RADA) 4GPRGDSGYRGDS-NH2) (KLT Ac-(RADA) 4G4KLTWQELYQLKYKGI- NH2)	In vitro studies; hDPSCs were isolated from extracted premolars and third molars without caries or periodontal diseases. Human umbilical vein endothelial cells (HUVECs) were obtained from the Chinese academy of sciences (category number: EAhy926). Rat DPSCs (rDPSCs) were isolated from the lower incisors of 3-weeks- old male sprague-dawley rats. Cell adhesion, viability, proliferation, morphology, and odontogenic differentiation assay were performed. Angiogenesis-inducing Activity of hDPSCs/SAP-Conditioned Medium in Matrigel matrix. In vivo; thirty-five 8-week-old male sprague-dawley rats divided into 7 groups (n = 5 animals per group). In groups, 1 through 6, the dental pulp under the occlusal surface of the left upper first molar was exposed and partially pulpotomized the residual pulp was implanted with one or a mixed SP with rDPSCs for 28 days	Shows an enhanced regenerative and reparative effect on a pulpotomized molar rat model, achieving pulp recovery and dentin regeneration	Xia et al. (2020)
Multidomain peptide (MDP)	An ex vivo mandible organ culture model was used. MDP hydrogel scaffolds were injected either at the interface of the odontoblasts and the dentin or into the pulp core of mandible slices and subsequently cultured for up to 10 days. Histological (alizarin red staining) and immunohistochemical analysis (dentin sialophosphoprotein, (collagen III, MMP2) were performed	Scaffolds design and self-assembly, release/ delivery, and bioactivity	Moore et al. (2015); Seyhan, 2019, (172)
Calcitonin gene-related peptide (CGRP)	Commercially available DPSCs were treated with varying doses of CGRP, and metabolic activity, viability, proliferation, and cell death were evaluated using 3-(4,5-dimethylthiazol-2yL)-2,5-diphenyl tetrazolium bromide assays, trypan blue staining, 5-bromo2′-deoxyuridine cell proliferation assay, and caspase-3 staining, respectively. DPSC differentiation was assessed with alizarin red staining and by quantifying messenger RNA expression of odontoblast makers	Mediating neurogenic inflammation, vascular and innervation in the pulp, and healing of periapical lesions is extensively	Caviedesbucheli et al. (2008); Michot et al. (2020)

grown enamel-like layer exhibits well-regulated crystal growth and improved composition, structure, and mechanical properties of artificial enamel (Yarbrough et al., 2010; Buzalaf et al., 2017; Prajapati et al., 2018; Bröseler et al., 2020; Farooq and Bugshan, 2020).

The tyrosine-rich peptides (TRAP) domain derived from amelogenin N-terminus has been associated with matrix self-assembly meanwhile, the amelogenin central polyproline repeat region could control crystal spacing, and the hydrophilic C-terminus facilitates amelogenin protein solubility and its adhesion to the crystal surface (Han et al., 2017; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Wang et al., 2020). On the other hand, leucine-rich peptides (LRAP) can promote both, enamel crystal nucleation and growth in mouse models (Ding et al., 2020). LRAP improves the remineralization of enamel surface lesions on extracted teeth in vitro more effectively than full-length amelogenin (Han et al., 2017; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Wang et al., 2020) and has been modified with phosphorylation using a calcium and phosphate-rich solution forming spherical nanoparticles in a linear chain-like pattern. These self-assembled peptides formed spherical amorphous calcium phosphate (ACP) particles and triggered ACP to hydroxyapatite phase transformation (Ieong et al., 2011; Bagheri et al., 2015; González-Cabezas and Fernández, 2018; Arifa et al., 2019; Mukherjee et al., 2019; Pandya and Diekwisch, 2019; Dissanayake et al., 2020; Farooq and Bugshan, 2020).

There is also an amelogenin repeat-based peptide that consists of 22-residues in five tandem polyproline repeat (GLn-Pro-X) and a seven residues hydrophilic tail. This peptide has shown the ability to promote the remineralization of enamel caries in an in vitro pH-cycling system. Besides, it could bind on the enamel

surface, and can stabilize ACP, meanwhile is able to control the crystallization of HA, and promotes the remineralization of caries lesion (Lv et al., 2015; Han et al., 2017; Kind et al., 2017; Mukherjee et al., 2019; Ding et al., 2020). Finally, the chimeric peptide Ame-CT16-HA6-1 is formed by 16 carboxyl-terminal residues of amelogenin attached to a sequence of SVSVGMKSPRR denominated HA6-1. This peptide in combination with carboxymethyl chitosan and ACP forms enamel-like apatite crystals and binds to demineralized enamel specifically to achieve rapid remineralization (Chung and Huang, 2013; Chung and Li, 2013; Kind et al., 2017; Xiao et al., 2017; Ding et al., 2020).

An important non-amelogenin protein synthesized by ameloblast is tuftelin, which induces and regulates the initial mineralization of enamel owing to its acidic nature. Tuftelin contains a self-assembly domain near the C-terminus and an anionic domain near the N-terminus that could be involved in the initial crystallization of enamel. The tuftelin derived peptide (TDP) has a significant effect on the nucleation of HA and remineralization of initial carious lesions *in vitro*, suggesting that this peptide has the potential to regenerate the structure and mechanical properties of enamel (Chung and Huang, 2013; Chung and Li, 2013; Kind et al., 2017; Xiao et al., 2017; Ding et al., 2020).

On the other hand, a dentin phosphoprotein (DPP)-derived peptide constituted of octuplet repeats of aspartate-serine-serine (8DSS), has been applied to the enamel surface to prevent leaching of ions from the enamel surface and to promote the uniform deposition of nanocrystalline calcium phosphate over demineralized enamel surface given that this peptide possesses the ability to bind calcium and phosphate ions from the saliva (Yarbrough et al., 2010; Hsu et al., 2011; Buzalaf et al., 2017; Bröseler et al., 2020; Farooq and Bugshan, 2020). When 8DSS is combined with fluoride shows a more effective synergistic interaction to inhibit demineralization, reducing the concentration of fluoride used to prevent caries. (Hsu et al., 2011; Chung and Huang, 2013; Chung and Li, 2013; Yang et al., 2014; Yang et al., 2016; Alkilzy et al., 2018a; Ding et al., 2020). Finally, an NSS peptide is obtained when an aspartate is replaced for asparagine from the DSS sequence of DPP. NSS enhances the formation of HA crystals onto the enamel surface when compared whit non-peptide treatment (Chung and Huang, 2013; Chung and Li, 2013; Kind et al., 2017; Xiao et al., 2017; Ding et al., 2020).

Peptides Non-Derived from the Amino Acid Sequence of Enamel and Dentin Proteins

Several studies have shown that specific salivary proteins such as histatin, statherin, mucins, and cystatins play an important role to protect against dental caries (Buzalaf et al., 2017; Valente et al., 2018; Arifa et al., 2019; Wang et al., 2020). For instance, statherin derived peptides containing at least 15 N-terminal residues (StN21 and StN15) bind to HA and enhance remineralization (Buzalaf et al., 2017; Valente et al., 2018; Arifa et al., 2019). Also, the statherin-derived peptide (DpSpSEEKC) can act as a nucleation template and can gather calcium ions to a high

concentration given its secondary structure or its negatively charged groups when is incubated in artificial saliva (Yang et al., 2017).

Another studied peptide is the elastin-like polypeptide (E125) which is rich in acidic amino acids and can stabilize ACP, and induces the orientation of crystal growth along the original enamel apatite nano-crystals, resulting in regeneration of the enamel apatite crystal structure including both the prismatic and inter-prismatic structures in oral simulated environment (Lv et al., 2015; Han et al., 2017; Zhou et al., 2018).

Self-Assembled Peptides

Regarding self-assembled peptides, these can form a three-dimensional scaffold and can promote early caries/white lesion remineralization (Pandya and Diekwisch, 2019; Bröseler et al., 2020; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Li et al., 2020). For instance, P11-4 is an N-terminally acetylated, C-terminal amidated, 11 amino acid residue peptide. This β-sheet forming self-assembling peptide possesses anionic groups in the side chains that attract Ca^{2+} ions, diffuses well into the body of the caries lesions due to its low viscosity, and triggers self-assembly within the lesion inducing the precipitation of HA *in situ*. A single application of P11-4 improves the appearance of white spot lesions after 180 days in a small-scale clinical study (Alkilzy et al., 2018a; González-Cabezas and Fernández, 2018; Arifa et al., 2019; Jablonski-Momeni et al., 2019; Üstün and Aktören, 2019; Kamal et al., 2020; Li et al., 2020). However, more evidence is still needed before this peptide can be used in caries prevention and regular therapy (Alkilzy et al., 2018a; González-Cabezas and Fernández, 2018; Arifa et al., 2019; Jablonski-Momeni et al., 2019; Üstün and Aktören, 2019; Kamal et al., 2020; Li et al., 2020).

In the case of the fourth-generation polyamidoamine dendrimer (PAMAM-Po3H2) which mimic the self-assembly behavior of amelogenins, it is used as an organic template to induce crystal remineralization with the same structure, orientation, and mineral phase of the intact enamel in a relatively short time (Brunton et al., 2013; Kind et al., 2017; Alkilzy et al., 2018b; Arifa et al., 2019; Pandya and Diekwisch, 2019; Üstün and Aktören, 2019; Bröseler et al., 2020; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Wang et al., 2020). Another strategy is to form films by amyloid-like lysozyme to obtain β-sheet stacked, which are combined with synthetic peptide based on the functional domains of C-terminal of amelogenin to promotes the oriented growth of HA crystals, which have a hardness and interfacial bonding stability higher than those of enamel repaired by fluoride. (Brunton et al., 2013; Kind et al., 2017; Alkilzy et al., 2018b; Arifa et al., 2019; Pandya and Diekwisch, 2019; Üstün and Aktören, 2019; Bröseler et al., 2020; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Wang et al., 2020).

ID4 and ID8 are peptides with shorter and optimized sequence patterns that are programmed to self-assembly into predefined conformations and nanostructures and in combination with hydrogels could serve as the template to induce HA nucleation and promote biomimetic remineralization of initial caries lesions. (Brunton et al., 2013; Kind et al., 2017; Alkilzy et al., 2018b; Arifa et al.,

2019; Pandya and Diekwisch, 2019; Üstün and Aktören, 2019; Bröseler et al., 2020; Dissanayake et al., 2020; Farooq and Bugshan, 2020; Wang et al., 2020).

Dentin

Dentin comprises the major mineralized part of the tooth and it is cover and protected by enamel in the tooth crown and surrounded by cementum in the radicular portion. The responsible cells in the dentin formation are the odontoblast, these cells are long-living post-mitotic cells (comparable to cardiomyocytes and neurons in the fact that they are stable and are not replaced throughout the whole life of a tooth) (Sasaki and Garant, 1996; Goldberg et al., 2011; Kawashima and Okiji, 2016). Its inorganic matrix is composed of HA crystals while its organic matrix is mainly composed of a collagenous structural component, formed of collagen type I (about 90%), collagen type III and V, and a small quantity of organic matrix molecules (proteoglycans of chondroitin sulfate (biglycan and decorin), heparan sulfate (perlecan and entactin), keratan and dermatan sulfate. It has also non-collagen proteins that participate in the mineralization process. These proteins are members of the SIBLING family (small integrin-binding ligand N-linked glycoprotein) and include the sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP-1), osteopontin (OPN), matrix extracellular phosphoglycoprotein (MEPE), and integrin-binding sialoprotein (IBSP) (Huang et al., 2008; Zhang et al., 2010) Due to odontoblast specifically expresses DSPP and DMP-1, these proteins are considered specific markers for these cells (Staines et al., 2012).

The dentin-pulp complex regeneration has two major limitations: 1) When the reactionary dentin has been formed, is permeable and fragmentable, resulting in microorganisms recontamination. This problem is caused by the poor attachment of the biomaterials to the dentin and lack of dental pulp stem cells (DPSCs) induction. 2) The second limitation is the pulp necrosis which avoids the blood supply to the exposed wall. The approach to overcome these problems is to create strategies to improve the adhesion of the biomaterials to dentin, promoting the HA nucleation, and the development of scaffolds with molecules that provide signals for dentinogenesis (Piva et al., 2014; Fawzy El-Sayed et al., 2019; Moussa and Aparicio, 2019). In this regard, the development of peptide therapies and biomaterials functionalized with peptides to promote dentinogenesis in the dentin-pulp complex are increasing and are presented below.

Casein Phosphopeptide with Amorphous Calcium Phosphate (CPP-ACP)

This agent is based on a nano-complex of the milk protein casein-phosphopeptide (CPP) combined with ACP and it has been used for the prevention of demineralization and enhancement of remineralization of enamel and dentin lesions (Rahiotis and Vougiouklakis, 2007). Its mechanism of action involves the fixing of calcium phosphate under neutral or alkaline pH solutions and promoting their assembling in HA on the dentin surface. Its biological mechanism allows the replacement of the minerals in the intra and interfibrillar

collagen spaces after demineralization is covered with CPP-ACP and incubated with artificial saliva. The experimental result of this therapy over dentin samples of extracted intact human third molar is the enhancement of the bond strength at the resin/dentin interface during the restorative intervention (Cao et al., 2013; Sattabanasuk et al., 2014). Nevertheless, the results do not reflect what occurs at the bonding interface in a clinical situation since some conditions cannot be replicated *in vitro* such as the volume of cement or cement thickness, the surface area of adhesion, and the cavity configuration.

Self-Assembling Peptide P11-4

P11-4 is a rational designed biomimetic peptide that has self-assembling behavior into beta-sheet fibrillar hydrogel at pH <7 (Koch et al., 2018). This peptide attracts calcium ions and form HA crystals from supersaturated solutions such as saliva and binds to collagen I in dentin tissue acting as a protector against proteolytic activity of collagenases in artificial dentin caries. These characteristics show that this peptide could be as a pretreatment of caries-affected dentin enhancing significantly the performance of the bond interface over time (de Sousa et al., 2019).

RAD/KLT Peptide

KLT peptide is formed by the amino acids 17–25 of the vascular endothelial growth factor (VEGF) and activates VEGF receptors inducing angiogenesis (D'Andrea et al., 2005). When this peptide is coupled to the beta-sheet self-assembling peptide RAD (Ac-RADARADARADA) to create the RAD/KLT peptide (Ac-$(RADA)_4G_4$KLTWQELYQLKYKGI- NH_2) forms, a gel of nanofibers of 16 nm that induces the odontoblastic differentiation from DPSCs. When this peptide is mixed with the self-assembling PRG peptide (Ac-$(RADA)_4$GPRGDSGYRGDS-NH_2), provides binding motifs for integrins by directly coupling a 2-unit RGD binding sequence to RAD (Xia et al., 2020). DPSCs grown on RAD/PRG/KLT shows improved survival and can be differentiated to angiogenic and odontogenic phenotypes *in vitro*. Histological and functional evaluations of a partially pulpotomized rat model showed its capability to stimulate pulp and dentin regeneration *in vivo* over the course of 28 days (Xia et al., 2020).

Derived Peptides from Calcium Phospholipid-Binding Protein, Copine 7 Protein (CPNE7)

The CPNE7 is a member of the family CPNE proteins which are Ca^{2+} dependent and phospholipid-binding proteins (Creutz et al., 1998), it induces reparative dentin and odontoblast differentiation from mesenchymal stem cells (Choung et al., 2016; Seo et al., 2017). Given its short half-life, some bioactive peptides derived from the sequence 321–360 (STTFEEMQKA FEEGQAQWDC VNPKYKQKRR SYKNSGVVL) region of CPNE7 have been developed. CPD4: VNPKYKQKRR, have shown an enhanced cell-penetrating activity as well as osteogenic efficiency in DPSCs. It also induces the expression of biomineralization markers *in vitro* and when is mixed with collagen gel, forms mineralized tissue in the calvaria rat defects model. These results suggest that CPD4 peptide has the potential to be used as a biotechnological material to

regenerate mineralized tissues like bone and dentin (Lee et al., 2019).

Dentonin

Dentonin or AC-100 is an SP derived from the central region of MEPE protein (residues 242–264: TDLQERGDNDISPFSGDGQPFKD). This peptide includes an integrin-binding sequence (RGD), a glycosaminoglycan-attachment sequence (SGDG), and a calcium-binding motif (Six et al., 2007). Dentonin peptide stimulates human bone marrow stromal cell proliferation and differentiation into osteoblast precursors and enhances dental pulp stem cell proliferation *in vitro* (Liu et al., 2004; Nagel et al., 2004). Also, it has been shown that agarose beads soaked with a solution of 5 mg dentonin/0.5 ml PBS and implanted into rat molars pulps promote pulp cell proliferation and reparative dentin formation at day 8, suggesting that dentonin promotes the regeneration of damaged dentin (Six et al., 2007).

Dental Pulp

The dental pulp is a soft ecto-mesenchymal tissue surrounded by dentin and it is highly vascularized and highly innerved. It consists of 75% water and 25% organic material. It contains a heterogeneous population of cells such as fibroblastic cells, stem cells, capillary blood vessels, peripheral nerves, lymphatic elements, as well as cells from the immune system, extracellular matrix represented by fibers, and fundamental substance. Collagen fibers are concentrated to form supporting elements for blood vessels and nerve trunks that course from the root apex to the coronal pulp chamber (Garant, 2003; Yoshida et al., 2020).

The pulp tissue is unique given its volume and its confinement within the dentin. It has little blood supply, except in the apical foramen, and lacks collateral blood supply, hindering infection eradication by the immune system (Yoshida et al., 2020). Dental pulp is an important component of teeth and plays important roles in 1) forming the dentin: this is the essential function of the pulp and it is maintained as long as the pulp is vital. The cells in charge of producing it are the odontoblasts. Depending on the moment in which it is produced, different types arise: primary, secondary and tertiary, 2) nutrition: the pulp is responsible for nourishing the dentine through the odontoblastic extensions and metabolites coming from the pulp vascular system, 3) sensitive: in the face of stimuli, aggression or pain, the pulp is capable of responding; in the sensitivity of the pulp, no matter the nature of the stimulus, there will always be a painful response, and 4) defense/repairing: it includes the ability to form dentin in the face of aggression (Zero et al., 2011; Mu et al., 2020).

Dental pulp is considered one of the most difficult tissues to regenerate given the loss of fibrous connective tissue and its anatomical distribution. The process of pulp regeneration begins with the revascularization as it plays a fundamental role in the reparative processes of dentin tissues and the homeostasis of the dentin-pulp complex itself (Saghiri et al., 2015; Kim, 2017; Jung et al., 2019). In the field of regenerative

endodontics, the most important point is to provide a favorable environment to achieve the regeneration of the lost tissues. Thus, crucial factors such as cells, scaffolds, and signaling molecules are required.

Peptides for Dentin-Pulp Complex Regeneration

SLd peptide is a minimally invasive injectable peptide scaffold that was developed from Dentonin sequence and demonstrated to be a self-assembled platform to support DPSCs and stromal cells in a biomimetic hydrogel environment. This peptide supports the proliferation of DPSCs and increases calcium phosphate deposition being cytocompatible to other critical stromal cells found in the dental pulp (Nguyen et al., 2018).

In the case of LRAP plus amelogenin exons 8 and 9 peptide (LRAP 8, 9), it was used to determine their effects on odontoblasts and dental pulp cells (DPCs). *In vitro* LRAP 8, 9 demonstrated to promote DPCs proliferation and differentiation to a greater extent than LRAP. These data suggest that amelogenin exons 8 and 9 may be useful in amelogenin-mediated pulp repair cell proliferation (Huang et al., 2012).

Another peptide is Cpne7-DP, which can be placed on 0.5% fibrin gel and then transplanted subcutaneously into immunocompromised mice. Twelve weeks after the transplantation, the Cpne7-DP treatment group showed the formation of dentin-pulp-like tissue with cells inserting long cellular processes into the tubule-like structure formed within newly mineralized tissue (Lee et al., 2020).

Peptide Scaffolds

The self-assembling peptide hydrogel PuraMatrix™ is a repeating polymer of the amino acid sequence RADA and is formulated as an injectable scaffold that assembles into nanofibers when is exposed to physiologic concentrations of salts. The SP has been used to investigate the role of DPSCs in triggering angiogenesis and the potential to regenerate vascularized pulp *in vivo*. The nanofiber microenvironment provided by this SP enables cell survival, cell migration, and capillary network formation in the absence of exogenous growth factors. Besides, an *in vivo* study shows that DPSCs increases early vascular network formation and increases VEGF expression in a mice model (Dissanayaka et al., 2015).

The RADA16-I sequence is a self-assembled peptide hydrogel that has amino acids positively (arginine) and negatively (aspartic acid) charged, and hydrophobic residues (alanine). It promotes the formation of hydrophobic and hydrophilic faces for B-sheets; it also promotes the migration of cells like DPSCs and the angiogenesis of human umbilical vein endothelial cells (Mu et al., 2020). Another SP is the functionalized scaffold RAD/PRG/KLT which shows an enhanced regenerative and reparative effect on a pulpotomized molar rat model, achieving pulp recovery and dentin regeneration *in vivo* (Xia et al., 2020).

The multidomain peptide (MDP) scaffolds can be used as injectables, bioactive, and biodegradable hydrogel scaffolds for tissue regeneration. It is a short sequence of amino acids that self-assemble to form fibers in an aqueous solution. The sequence K(SL)₃RG (SL)₃KGRGDS is compatible with the dental pulp and promotes differential responses depending on the cell type

(Moore et al., 2015). It has been shown that subcutaneous transplantation of the hydrogel within dentin cylinders into immunocompromized mice led to the formation of a vascularized soft connective tissue similar to dental pulp, supporting the use of this biomaterial as a candidate for regenerative endodontics (Galler et al., 2012).

Synthetic Neuropeptides

Neuropeptides are defined as peptide neurotransmitters or neuromodulators. Multiple studies have demonstrated that trigeminal afferent neurons express Calcitonin gene-related peptide (CGRP), which innervates the dental pulp and also increases the expression of proteins associated with dentine formation in human pulp cells. CGRP and substance P mediate neurogenic inflammation and contribute to reparative dentin production and pulp tissue regeneration (Caviedesbucheli et al., 2008; Michot et al., 2020).

PERIODONTAL REGENERATION

The concept of periodontium includes a set of tissues that comprise the root cementum, alveolar bone, gingiva, and a functionally oriented PDL. Periodontal tissue damage affects dental organ support; hence, gingivitis and periodontitis are commonly caused by trauma or bacterial infection (Elango et al., 2020). These diseases attempt against periodontium homeostasis, causing tooth-loss (Polimeni et al., 2000).

As for every dental tissue replacement, it is necessary to mimic the physical and mechanical properties of naturally formed tissues (Yen and Yelick, 2011). Another challenge for restoring damaged periodontium is the fact that the inductive microenvironment given during the formation of periodontal tissues, is not the same after total development of the tooth (Liang et al., 2020). Although structure and function could be partially restored (Liang et al., 2020) through enamel matrix, grafting materials, guided tissue regeneration technique (GTRT), the use of growth factors, and stem cells, all of them present difficulties to be successful. Since natural microenvironmental characteristics are almost impossible to imitate, research focuses on biomimetic systems that combine natural or synthetic molecules like peptides (**Table 2**), amino acids and even cells with diverse biomaterials to build cell-3D scaffolds that enhance cell-material interactions (Elango et al., 2020). SP could be used as scaffolds or signals to achieve periodontal regeneration (**Figure 2**).

Periodontal Ligament

The PDL is a specialized connective tissue located around dental roots and serves as an anchor to the alveolar bone, controls tooth homeostasis, allowing its reparation and nutrition (Tomokiyo et al., 2019). The PDL consists of well-organized collagen fibers that anchor the root cement with alveolar bone, thus, is critical for periodontal regeneration (Liang et al., 2020). The extracellular matrix of these tissues is composed of members of the collagen family, proteoglycans, and a heterogeneous set of glycoproteins.

The PDL also acts as a sensory organ necessary for the proper positioning of the jaws during mastication with very high adaptability to rapid changes in applied forces and the capacity to maintain its width (McCulloch and Melcher, 1983). PDL fibroblasts are the dominant heterogeneous cell population in the PDL, being capable to differentiate into cementoblasts and osteoblasts (Roberts et al., 1982; McCulloch and Melcher, 1983). There is a low level of periodontal ligament stem cells (PDLSCs), which possess the capacity to differentiate into periodontal ligament fibroblasts, cementoblasts, and osteoblasts. In this regard, is important the distinction between PDLSCs and PDL fibroblast populations since PDLSCs are normally quiescent and can be only activated during tissue damage. Other cell types include the epithelial cell rests of Malassez, monocytes, macrophages, cementoblasts, osteoblasts, fibroblasts, myofibroblasts, nerve cells, epithelial cells, and endothelial cells (Barczyk et al., 2000; Bartold et al., 2000). Thus, PDL is a complex tissue and its regeneration is hampered since it is mandatory the control of infection and inflammation to then promote cell adhesion, proliferation, and differentiation for new tissue formation (Liang et al., 2020).

One of the first attempts for restoring PDL was the use of Enamel matrix derivative (EMD) obtained from animal tissue. Then, a synthetic oligopeptide derived from EMD was developed, showing enhancement of proliferation of PDLSCs (Kato et al., 2013). However, its functional mechanisms are still not entirely clear.

Another extensively studied peptide is the tri-amino acid sequence, arginine-glycine-aspartate (RGD) which has been demonstrated to improve the attachment of several cell types to different materials (Hautanen et al., 1989; Aota et al., 1994). Besides, RGD mixed with extracellular matrix (EMC) proteins, reduces the risk of immune reactivity or pathogen transfer (Bellis, 2011), and *in vitro* studies has shown that synthetic RDG conjugated with poly-L-lysine backbone and oligo-DL-alanine or with L-serine-oligo-DL-alanine increases cell adhesion and migration of PDL-derived cells, which is promising for periodontal regeneration (Khorolsuren et al., 2020). Also, the integrin-binding cyclic and linear synthetic RGD-EPRGDNYR has shown enhancement of attachment, cell proliferation, and spreading of PDLC, being the cyclic forms of EPRGDNYR-BSA the most effective (Grzesik et al., 1998). A fibronectin peptide containing their RGD and PHSRN sequences coupled with six glycines (G3PHSRNG6RGDG) is able to enhance attachment and spreading of human PDLC by increasing ERK1/2 activity. This SP could be used to improve the environment for PDLC and achieve periodontal regeneration (Kim et al., 2004).

The ameloblastin-derived peptide (VPAFPRQPGTPGVASL) was first related to an increase in cell attachment and proliferation of PDL cells (PDLC), acting as a growth factor during periodontal regeneration (Zeichner-David et al., 2006). Recent studies do not show effects over proliferation of PDLC, but a stimulating effect on the mineralization capacity of PDLC (Kitagawa et al., 2011).

A peptide matrix named dendritic lysine-appended polydiacetylene (Lys-PDA) has shown the promotion of cell

TABLE 2 | Synthetic peptides used in periodontal tissues regeneration.

PERIODONTAL LIGAMENT			
Peptide	**Methodology**	**Effect**	**References**
Oligopeptide derived from EMD (OP-EMD) (WYQNMIR)	*In vitro* study with human mesenchymal stem cells. Solid-phase peptide synthesis + "tea-bag" methodology, cell proliferation assay, alkaline phosphatase activity, measurement of procollagen type 1 C-Peptide, osteocalcin production, mineralization assay, extracellular signal-related kinases (ERK) were performed	Enhanced proliferation of PDL cells, as well as ALP activity, expression of osteonectin, osteocalcin production, the formation of calcified nodules, and mineralization	Kato et al. (2013)
Integrin-binding cyclic and linear synthetic RGD-EPRGDNYR. (EPRGDNYR) linear and cyclic	*In vitro* study with human PDLSCs. PDL cells adhesion, proliferation, and the *novo* protein synthesis *in vitro*	For attachment, cell proliferation, and spreading, the cyclic forms of EPRGDNYR-BSA conjugate were most potent than linear conjugate. The effects of all collagen/conjugate mixtures were equivalent to that of type I collagen	Grzesik et al. (1998)
Fibronectin peptide containing their RGD and PHSRN sequences coupled with six glycines (FP-RGD-PHSRN) (G3PHSRNG6RGDG)	*In vitro* study with human PDL cells. The cells were applied to peptide-coated wells at a density of 1×10^{4}/well. After 1 h incubation at 37°C, adhered cells were fixed, stained, and examined by phase contrasts microscopy for cell spreading assay. The attached PDL cells were solubilized with 2% sodium dodecyl sulfate (SDS) for the cell attachment assay by measuring absorbance at 595 nm in a microplate reader. Western blot analysis was performed to determine extracellular signal-regulated kinase (ERK1/2) activity	Enhances attachment and spreading of human PDLC by increasing ERK1/2 activity	Kim et al. (2004)
Ameloblastin peptide, based on the 16 amino acid sequence of the N-terminal porcine ameloblastin. (AMB-DP) (VPAFPRQPGTPGVASL)	*In vitro* study with PDLC. Ameloblastin peptide synthesized by a pink technology method, cell proliferation assay, and alkaline phosphatase activity, inhibition assay with anti-ameloblastin antibody, mineralization assay, and RT-PCR were performed	Increase in cell attachment and proliferation of PDL cells. Stimulates ALP activity in a dose-dependent manner, promotes mineralized nodule formation by PDL cells, and upregulates ALP and bone sialoprotein (BSP)	Zeichner-David et al. (2006); Kitagawa et al. (2011)
Dendritic lysine-appended polydiacetylene (Lys-PDA)	*In vitro* study with human PDLSCs. hPDL cell viability, adhesion, and spreading on Lys-PDA, FDA/PI live/dead assay, MTT assay, actin cytoskeleton staining, osteogenic differentiation, and alizarin red staining were performed	Supports periodontal cell adhesion and differentiation. The functionalized electrospun PCL mat also promoted cell viability, adhesion, and spreading	Das et al. (2019)
HydroMatrix (HydM)	*In vitro* study with human PDLSCs. Measurement of adhesion and proliferation using real-time impedance analysis, cell viability assay, cell morphology studies, osteogenic differentiation, and real-time RT-PCR.	PDL cells can adhere, migrate, survive, proliferate, and differentiate into the osteogenic direction on the HydM gel	Nagy et al. (2018)
ALVEOLAR BONE			
Peptide	**Methodology**	**Effect**	**References**
Osteogenic growth peptide (OGP ())	In vitro studies include; cell isolation and primary osteogenic cell cultures, cell morphology, cell proliferation and viability, evaluation of total protein content, ALP activity, and mineralized matrix formation In vivo studies include a surgical protocol where 60 male adult rats divided into three experimental groups with five animals each: Group I (GI): BC and BC OGP (10–14), group II (GII): BC-COL and BC-COL OGP (10–14) and group III (CG): Negative control group (no treatment) for periods at 1, 2, 4 and 16 weeks with a noncritical size bone defect (2 mm) in the femur. Histological, radiographic, and histomorphometric analyses were performed	Promotes proliferation, differentiation, and biomineralization of osteoblastic linage cells	Saska et al. (2018)
BMP-2 peptide (BMP-2P) (KIPKASSVPTELSAISTLYLGGK)	In vitro cytotoxicity assessment with the MTT assay using L929 mouse areolar fibroblasts In vivo critical-sized alveolar defect model with sprague dawley rats. A standardized tooth extraction rodent model was used, and post extraction the defects were either filled with graft materials for the experimental groups or left unfilled for the control group. Radiographic and histopathological analyses were performed	Osteogenic differentiation and biomineralization	Boda et al. (2019)

TABLE 2 | (*Continued*) Synthetic peptides used in periodontal tissues regeneration.

ALVEOLAR BONE

Peptide	Methodology	Effect	References
Peptide derived from parathyroid hormone residues 1–34. (PTH1-34)	In vitro, the expression of TNF-α, IL-1β, and IL-6 was assessed by immunohistochemistry and western blot. In vivo diabetic rats were treated subcutaneously with low-dose (40 µg/kg, once daily for 5 days per week), middle-dose (80 µg/kg) or high-dose (160 µg/kg) PTHrP1-34 peptide. Treatment continued for 12 weeks. Changes in periodontal tissues were confirmed by micro-computerized tomography assay and H&E analysis	Bone mineralization and an inhibitory effect on alveolar bone resorption	Zhang et al. (2017)
AMB/P-15	In vivo 7 mm diameter fenestrations were made with a trephine in the mid-root of both maxillary canines in each dog. Bone, periodontal ligament, and cementum were removed. Block sections were retrieved at 3 and 8 weeks for histologic processing	Enhance fibroblast attachment with greater regeneration of fenestration defects	Vastardis et al. (2005)
CGRP	In vitro Quantitative real-time RT-PCR was performed for embryonic CGRP, VEGF-A, CD31, Col I, Col II, OPN, MMP-2, LYVE-1, and GAPDH. Also In situ hybridization of murine CGRP and VEGF-A. In vivo, they used mandible and tibia mouse at various times (E12.5, E14.5, E17.5, E18.5, P0, P1, and P5), then isolated total RNA and performed a RT-PCR	Biomineralization and vascularization	Maeda et al. (2017)
RGD	In vitro PDL cell cytotoxicity was tested with 3-[4, 5- dimethylthiazol-2yl]-2, 5-diphenyl-2H-tetrazolium bromide assay. Cell migration toward the chitosan-based materials was analyzed with a trans-well migration assay. In vivo Horizontal periodontal defect model was created in four maxillary and mandibular lateral incisors of Macaca nemestrina. Following periodontal therapy, the sites were transplanted with various regenerative materials: 1) chitosan, 2) RGD-modified chitosan, 3) PDL cell sheet with chitosan, 4) PDL cell sheet with RGD-modified chitosan. The periodontal tissue regeneration was evaluated clinically and radiographically. Gingival crevicular fluids were collected each week to evaluate cementum protein-1 (CEMP-1) expression with enzyme-linked immunosorbent assay, while the biopsies were retrieved after 4 weeks for histological and microcomputed	Higher alveolar bone density, as well as higher CEMP-1 protein expression. Adhesion and proliferation of osteoblasts	Amir et al. (2020)
HydroMatrix	In vitro study with human PDLSCs. Measurement of adhesion and proliferation using real-time impedance analysis, cell viability assay, cell morphology studies, osteogenic differentiation, and real-time RT-PCR.	Osteogenic differentiation of PDLSCs	Nagy et al. (2018)

RADICULAR CEMENTUM

Peptide	Methodology	Effect	References
CEMP-1-p1	*In vitro* nucleation assay is a slow and controlled chemical reaction between the calcium and phosphate ions (without organic matrix) in a semisolid medium made of sodium metasilicate solution polymer at physiological pH and room temperature	This peptide has been related to the formation of spherical mineral structures on a nanometric scale and with a well-defined growth center of octacalcium phosphate, a precursor of HA.	Correa et al. (2019)
Amelogenin-derived peptide 5 (ADP5)	*In vitro* studies where an alkaline phosphatase based mineralization model was used to investigate the mineralization behaviors of the peptides. Cell adhesion and proliferation experiments were accomplished using cultured human periodontal ligament (hPDL) fibroblasts. *Ex vivo* studies where the cementum-root stock blocks were prepared from single-rooted, extracted adult teeth. Cylindrical blocks of 4 mm diameter were cut from the acellular cementum, close to the cementoenamel junction the specimens were coated with the peptide and incubated. The mechanical properties of the cementomimetic layer were assessed by nanoindentation and qualitative mechanical abrasion tests	Facilitate cell-free formation of a cementum-like hydroxyapatite mineral layer on demineralized human root dentin that supported attachment of periodontal ligament cells	Gungormus et al. (2012)

TABLE 2 | (Continued) Synthetic peptides used in periodontal tissues regeneration.

RADICULAR CEMENTUM

Peptide	Methodology	Effect	References
BMP-6p	In vivo studies in a rat model where surgery to create a bony window on the buccal aspects of mandibular molar roots were performed. 24 male sprague dawley rats were divided into four groups according to BMP application (0, 1, 3, and 10 microg, respectively). Animals were killed after 28 days and the mandible was taken for histological examination. Histometric measurements were performed on sections selected from three levels (coronal, middle, and apical levels; with 240 μm apart from the central) of the defect. New bone and cementum formation (including area and thickness) were analyzed and compared	Induces the formation of cellular cementum-like tissue, with Sharpey's fiber attachment after 28 days in a rat model	Huang et al. (2005)
ABM/P-15	Case report a maxillary lateral incisor with advanced adult periodontitis that was treatment planned for extraction was treated with sulcular incisions, full-thickness flap reflection, debridement of granulomatous tissue from the defect, placement of a notch in the root at the apical extent of calculus, mechanical root planing, brief cleansing with citric acid, grafting with abm/p-15, wound closure with sutures, and placement of a periodontal dressing. Biweekly to monthly recalls were made until removal of a small block section biopsy at about 6 months	In a human case shown favorable histologic healing, including cementum, PDL, and alveolar bone on a previously calculus and biofilm contaminated zone	Yukna et al. (2002)
Synthetic anabolic peptide (AP)	In vivo study where periodontal defects were created bilaterally adjacent to four mandibular teeth in five baboons. The plaque was allowed to accumulate around wire ligatures placed into the defects. After 2 months, the wire ligatures were removed, and a notch was placed at the base of the defect. The four teeth were randomly treated with one of the following treatments: 1) saline + ACS serving as the control, 2) AP + ACS, 3) saline + beta-TCP serving as another control, or 4) AP + beta-TCP. The baboons were sacrificed 5 months post-treatment, and histomorphometric analyses were performed under masked conditions	Induces new cementum formation by the stimulation of cell activity on the root surface	Yamashita et al. (2010)

GINGIVA AND OTHER SOFT TISSUES

Peptide	Methodology	Effect	References
P2 (PLVPSQPLVPSQPLVP SQPQPP LPP)	In vivo study has a split-mouth, randomized, placebo-controlled design. Test and control wounds were created on the palatal mucosa of 54 sprague-dawley rats. Wounds were histologically processed, and re-epithelialization, leukocyte infiltration, and angiogenesis were assessed at days 1, 3, and 7 post-surgery	Promotes epithelial migration, induces reduction of inflammation, increased angiogenesis, and accelerated wound closure in the oral mucosa	Villa et al. (2015)
KSL-W (KKVVFWVKFK)	In vitro normal human gingival fibroblasts were cultured. t Of primary human gingival fibroblasts were incubated with different concentrations (0, 10,50, or 100 μg/ml) of peptide KSL-W and used to evaluate the effect of KSL-W on the attachment (phase-contrast microscopy, stained F-actin filaments) cell cycle analysis, a trypan blue exclusion assay to determine viable cell numbers was performed. MMP-1, MMP-2, TIMP-1, and TIMP-2 protein levels were analyzed by ELISA. Type I collagen assay system was used to evaluate the effect of peptide KSL-W on collagen gel contraction by gingival fibroblasts	Promotes gingival fibroblast adhesion, cell growth and enhances the secretion of MMP1, MMP2, and α-smooth muscle actin	Park et al. (2017)
SV (SVVYGLR)	In vitro normal human-derived gingival fibroblasts (NHGF) and human oral mucosa keratinocytes (HOMK) were used for in vitro experiments. WST-1 assay. Either NHGF (3.0 × 104 cells) or HOMK (4.0 × 104 cells) were added into each well of 96-well plates and cultured in a medium containing SV peptide (20 ng/ml), rSV peptide (20 ng/ml), or phosphate-buffered saline (PBS). Fibronectin (10 μg/ml)-precoated 96-well microplates were used for the adhesion assay. The boyden chamber principle was applied for the cell migration assay. A standard scratch wound healing assay was adopted to evaluate the motility of NHGF or HOMK. In vivo study, a rat model was used. Male sprague–Dawley rats. An oral punch wound was prepared at the left buccal mucosa approximately 7–8 mm behind the angle of mouth. A 5-mm dermal biopsy punch was used for this purpose, and a full-thickness mucosal wound was created in each animal. After the preparation of the wound, SV peptide (20 ng/ml, n = 5), rSV peptide (20 ng/ml, n = 5), or PBS (n = 5) was dividedly injected into four sites of wound periphery as a total amount of 1 ml solution for each site. Immunohistochemical and photographic analyses were performed	Is implicated in angiogenesis, and fibroblast differentiation into myofibroblasts in oral mucosa regeneration	Tanaka et al. (2020)

adhesion and proliferation of isolated PDLC *in vitro*. However, by its structure, the main issue is to build a thick scaffold, and efforts are focused on finding a carrier material alternative to Lys-PDA (Das et al., 2019).

HydroMatrix (HydM; Sigma-Aldrich, St. Louis, MO, United States) is a nanofiber scaffold for tissue engineering which can self-assemble and shows ideal conditions for PDLSCs proliferation without morphological changes (Nagy et al., 2018).

Alveolar Bone

The alveolar bone is the portion of the maxilla and mandible that surrounds the teeth and represents the primary support structure for the teeth. Two of the main causes of alveolar bone loss are periodontitis and trauma (Fu and Yap, 2007). The procedures for the regeneration of the alveolar bone are mainly based on the use of natural or synthetic scaffolds and bioactive agents (Kao et al., 2015). However, there are some inherent limitations associated with biomaterials and traditional techniques (Soldatos et al., 2017). An interesting alternative is the design of biomaterials modified with bioactive peptides that can interact with the surrounding tissues through biomolecular recognition. As a treatment strategy, peptides offer many of the advantages of protein therapeutics while addressing some of their limitations (Jabbari, 2013).

Osteogenic Growth Peptide

Osteogenic growth peptide (OGP) is a naturally occurring molecule with a primary structure similar to the C-terminal end of histone H4, whose sequence contains a highly conserved 14 amino acid motif (Pigossi et al., 2016). Furthermore, OGP and OGP-(10–14) are potent regulators of marrow stromal cells, and as a soluble peptide, their main activity includes promoting proliferation, differentiation, alkaline phosphatase activity, and matrix mineralization of osteoblastic lineage cells (Chen et al., 2007; Fei et al., 2010; An et al., 2014). OGP has been incorporated into regenerative membranes used in the GTRT. For instance, it has been shown that membranes based on biopolymers combined with OGP-(10–14) stimulate the proliferation and activity of osteoblasts *in vitro*, as well as the repair of bone tissue *in vivo* (Saska et al., 2018). Both, *in vitro* and *in vivo* experiments showed that the material is beneficial for cell adhesion, has good biocompatibility, enhances the expressions of osteogenic-related genes, and accelerates bone regeneration. Moreover, a novel osteogenic polypeptide hydrogel-based in photo-cross-linked gelatin methacryloyl with photo-cross-linkable OGP has been proposed as a promising alternative for bone repair and regeneration (Qiao et al., 2020).

Peptides Derived From Bone Morphogenic Proteins

The bone morphogenetic proteins (BMPs) have great biomedical potential as osteogenic factors (McKay and Sandhu, 2002; Kelly et al., 2016). An attractive approach to reduce the BMPs side effects in bone regeneration such as bone overgrowth or immune response (Carragee et al., 2011), is to use peptides derived from the bioactive domains of rhBMP-2 or other osteoinductive proteins (Jabbari, 2013). Peptides derived mainly from BMP-2, BMP-7 and BMP-9 have been studied for their ability to promote

osteogenic differentiation *in vitro* and bone formation *in vivo* (Wang et al., 2017). It has been shown that human mesenchymal stem cells cultured on functionalized nanopatterned substrates with immobilized BMP-2 peptide (KIPKASSVPTELSAISTLYLGGK) exhibited greater potential for osteogenic differentiation (Kim et al., 2013). A previous study revealed that the application of mineralized nanofiber segments loaded with the E7-conjugated BMP-2 peptide in rat maxillae defects enabled a sustained peptide release over 4 weeks. Also, the X-ray microtomography analysis of peptide-loaded nanofiber graft filled defects revealed approximately three times greater new bone volume and density in comparison to unfilled control defects (Boda et al., 2019).

Parathyroid Hormone-Related Peptides

Parathyroid hormone (PTH) is considered as one of the major systemic regulators of calcium metabolism and bone remodeling (Goltzman, 2018). The peptide derived from PTH residues 1–34 (PTH1-34) is one of the earliest artificially synthesized amino acid fragments that was approved for the prevention and treatment of osteoporosis (Tashjian and Gagel, 2006). In a previous placebo-controlled clinical trial, PTH1-34 was associated with improved clinical outcomes, greater resolution of alveolar bone defects, and accelerated osseous wound healing in the oral cavity (Bashutski et al., 2010). It has been revealed that an RGD modified polyethylene glycol hydrogel containing PTH1-34 exhibited a clear beneficial effect on bone regeneration in circumferential bone defects around dental implants in a dog model (Jung et al., 2007). Besides, a recent study, showed that adding PTH1-34 to a xenograft increased the hardness of regenerated bone and accelerated bone mineralization in reconstructing mandible defects of pigs (Emam et al., 2020). Also, PTH1-34 may prevent alveolar bone resorption in type 1 diabetic rats, and that its intermittent administration could play an anabolic role in alveolar bone (Zhang et al., 2017).

Other Peptides

Peptide P-15 is a highly conserved peptide analog of the cellular binding domain of type I collagen (Bhatnagar et al., 1999). A previous research reported that the application of an organic bone mineral graft coated with a biomimetic collagen peptide (ABM/P-15) resulted in greater regeneration of fenestration defects in dogs at 8 weeks compared to controls (Vastardis et al., 2005). Additionally, it has been shown that ABM/P-15 associated with acellular dermal matrix, efficiently promotes the maintenance of the buccal-palatal dimension after tooth extraction in humans (Fernandes et al., 2011).

Another peptide that can be synthesized is the calcitonin gene-related peptide (CGRP) which is widely distributed in bone tissue and is known to be closely associated with osteogenesis (Maeda et al., 2017). Also, the RGD SP constitutes a system of cell surface signaling that enhances cell attachment and spreading of osteoblasts onto scaffolds and graft material (Durrieu et al., 2004). A recent study revealed enhanced regeneration of the horizontal periodontal defect in RGD-modified chitosan

macaque model, showing higher alveolar bone density than controls (Amir et al., 2020). Finally, HydM has even shown osteogenic differentiation on PDLSCs *in vitro*. Even though the study has shown the potential of the HydM scaffold, more studies *in vitro* and *in vivo* are needed (Nagy et al., 2018).

Dental Cementum

Dental cementum is a hard and avascular connective tissue located on the dental root, whose main function is to connect the fibers of the PDL that emerge from the alveolar bone to the dental organ. Two types of cementum can be distinguished according to the presence (cellular cementum) or absence of internal cells (acellular cementum). Their composition is distributed by approximately 50% of mineral matter, mainly HA $(Ca_{10} (PO_4)_6 (HO)_2)$ and 50% of organic matrix, being type I collagen 90% of the organic composition. Another cement-related collagen protein includes type III collagen, involved in the development, repair, and regeneration of periodontal support structures (Nanci and Bosshardt, 2000).

The participation of dental cementum in processes such as maintaining stability and chewing charge distribution is crucial. Thus, when cementum is affected by periodontal disease or trauma, periodontal therapy must provide a root surface free of etiological factors to promote the reinsertion of collagen fibers and avoid the formation of pathological spaces that promote bacterial proliferation. Therefore, the success of periodontal regenerative therapy relies on the dental cementum, its health, and its well-regenerative capacities (Grzesik and Narayanan, 2002).

There are two typical cementum-specific proteins. The 3-Hydroxyacyl coenzyme A dehydratase 1/Cementum Attachment Protein (HACD1/CAP), induces the nucleation, regulation, and direction of hydroxyapatite crystal growth and enhances regeneration of critical bone defects in rat calvaria. Cementum protein 1 (CEMP-1) (Arzate et al., 1992; Bermúdez et al., 2015; Villegas-Mercado et al., 2018) regulates the activity of cementoblasts by inducing differentiation and intervenes in the process of mineralization, migration, and proliferation of gingival fibroblasts. CEMP1 also promotes the nucleation of OCP crystals (Alvarez-Perez et al., 2006).

Peptides Derived from the Amino Acid Sequence of Cementum Proteins

Some SP derived from dental cementum proteins such as CEMP-1 (CEMP-1-p1) and HACD1/CAP (CAP-pi) have biological activity associated with the *in vitro* biomineralization (Correa et al., 2019; Montoya et al., 2019; Montoya et al., 2020). CEMP-1-p1 induces the formation of spherical mineral structures on a nanometric scale and with a well-defined growth center of OCP (Correa et al., 2019). CAP-pi shows inhibitory activity of mineral crystal nucleation and growth (Montoya et al., 2020). The behavior of CEMP1- derived peptides is related to their capacity to activate Wnt/β-catenin signaling pathways, which is associated with the enhancement of the biomineralization process (Arroyo et al., 2020).

Peptides Non-Derived from the Amino Acid Sequence of Cementum Proteins

The amelogenin-derived peptide 5 (ADP5) enhances cell-free formation of a cementum-like HA mineral layer on demineralized human root dentin that supports attachment of periodontal ligament cells *in vitro*. Additionally, ADP5 has shown a kinetic control over calcium phosphate nucleation governed by interactions with precursor ions attracting Ca^{2+} and PO_4^{3-} and creating an increased local supersaturation of those ions. Cell adhesion and cell proliferation assays on the surface of ADP5-mediated cementum-like tooth material showed that the mineral layer favors adhesion and proliferation of periodontal cells. Thus, the cementomimetic layer formed by ADP5 could have the potential clinical application to repair diseased root surfaces and promote the regeneration of periodontal tissues (Gungormus et al., 2012).

The synthetic BMP-6 polypeptide, induces a thicker formation of cellular cementum-like tissue, with the incorporation of Sharpey's fiber attachment when is applied to periodontal fenestration defect in rats, after 28 days of healing (Huang et al., 2005).

The ABM/P-15 SP has been used in a human histologic case demonstrating favorable histologic healing of cementum, PDL, and alveolar bone on a previously calculus- and biofilm-contaminated zone, demonstrating its regenerative potential (Yukna et al., 2002).

A 23-amino acid peptide that corresponds to the central region (242 through 264) of human MEPE, the synthetic anabolic peptide (AP) (Nagel et al., 2004) has effects on normal osteoblast precursor cells. When is combined with a-tricalcium phosphate and an absorbable collagen sponge as the carrier induces the formation of new periodontal tissue on the root surfaces, showing that the sites with AP have more cementum formation than control sites. These results suggest that AP may affect cementogenesis by stimulating cell activity on the root surface (Yamashita et al., 2010).

Gingiva and Other Soft Tissues

The gingiva is the oral mucosa that covers the alveolar bone and cervical part of the tooth. The gingiva is composed of a layer of epithelial tissue (divided into three functional compartments; gingival, sulcular, and junctional epithelium) and the connective tissue into superficial and deep compartments (Nanci and Bosshardt, 2000). The gingiva forms a physical barrier against oral bacterial and provides mechanical protection to the underlying tissues (Hassell, 2000). Given its protective nature, the gingiva is key for wound healing since is constantly exposed to trauma or bacterial products that lead to inflammatory and infectious events. (Häkkinen et al., 2000). Some authors claim that wound healing represents a conserved process while the cellular processes of oral soft tissue resemble the healing of skin wounds (Polimeni et al., 2000; Wikesjö and Selvig, 2000). Nevertheless, important differences occur since it is commonly stated that oral wounds heal better and with less scar formation than dermal wounds (Häkkinen et al., 2000; Sculean et al., 2014).

The normal response to injury involves three overlapping stages: 1) inflammation, 2) new tissue formation, and 3)
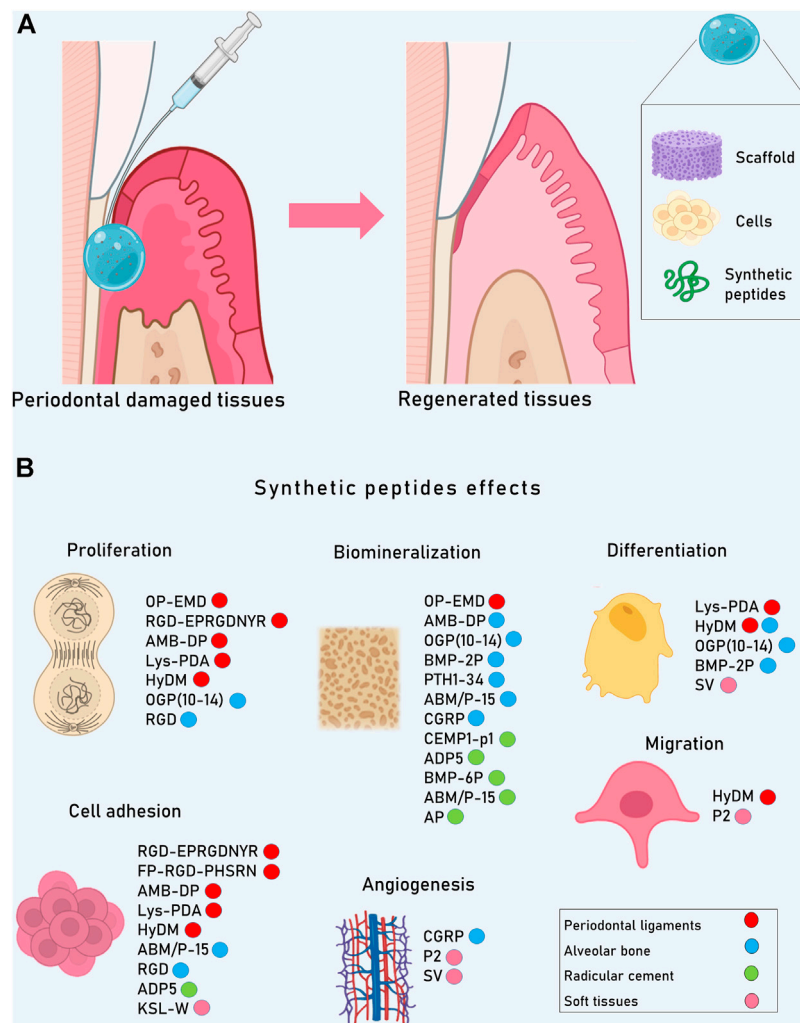
FIGURE 2 | Although the periodontium could be partially restored through tissue regeneration techniques, its complete regeneration is not possible yet since natural microenvironmental characteristics are almost impossible to imitate. **(A)** Research focuses on biomimetic systems that combine natural or synthetic molecules like peptides with scaffolds and cells to restore structure and function of the periodontal complex. **(B)** SP in periodontal cells are able to induce proliferation, migration, adhesion, angiogenesis, differentiation and biomineralization, enabling the formation of new tissue.

remodeling (Smith et al., 2015). After tissue injury, distinct biological pathways immediately become activated and are synchronized to prevent infection and restore the damaged tissues (Smith et al., 2015). The cells recruited during wound healing include components of the immune system, endothelial cells, keratinocytes, and fibroblast (Gurtner et al., 2008). In the last years, SP have arisen like a novel approach to enhance this process.

Synthetic Proline-Rich Peptide (P2)
The peptide P2 (PLVPSQPLVPSQPLVPSQPQPP LPP) was evaluated in a rat oral mucosal incisional wound healing model (Villa et al., 2015). P2 SP was previously shown to promote mesenchymal stem cell differentiation, induces bone formation, and mineralization *in vitro* (Ramis et al., 2012; Petzold et al., 2013). P2 enhances epithelial migration over the wound,

reduces inflammation, increases angiogenesis, and accelerates the wound closure. P2 peptide contains proline-rich sequences, which are related to the immune response, wound repair (Zanetti, 2004), and angiogenesis (Li et al., 2000).

Antimicrobial Peptide KSL-W
The synthetic decapeptide KSL-W (KKVVFWVKFK) has an antimicrobial effect, promotes gingival fibroblast adhesion by increasing F-actin production, enhances cell growth by increasing the S, and induces G2/M cell cycle phases. Besides, increases the secretion of MMP-1, MMP-2, and the expression of α-smooth muscle actin, inducing wound healing (in the wound scratch assay) at 50 and 100 μg/ml. Also, KSL-W induces activation/differentiation of gingival fibroblast to myofibroblasts at the wound site contributing to tissue repair (Park et al., 2017).

Synthetic Peptide SV

An osteopontin-derived 7-amino-acid (SVVYGLR) SV is implicated in angiogenesis and fibroblasts differentiation to myofibroblasts. SV peptide induces cell migration of oral fibroblast and keratinocytes by activation of TGF-β/Smad signaling pathway *in vitro*. *In vivo*, the SV peptide accelerates the healing process of oral mucosal wounds by facilitating angiogenesis and increasing the production of fibroblasts and myofibroblasts in a rat-oral wound model (Tanaka et al., 2020).

CLINICAL IMPLICATIONS AND SIDE EFFECTS

Until now, it is well-known that human dental tissues once formed cannot be biologically repaired or replaced. And their complex configurations demand different strategies for regeneration. In this regard, enamel and dentin require the use of cells in 3-D scaffolds for their eventual mineralization meanwhile pulp tissue requires processes such as revascularization and innervation. Thus, regenerative approaches and their potential clinical implementation remain a challenging task to achieve.

From a clinical perspective, SP combined with conventional treatments or alone can enhance remineralization or increase thickness and mechanical properties of the regenerated enamel and dentin. Furthermore, short peptides are not targeted for hydrolytic enzymes in the oral cavity, and some of them have minimal or null toxicity since their sequences are derived from natural proteins. Nevertheless, most of them remain under experimental investigation on *in vitro* cell models and preclinical models and have to be validated to determine their effectiveness, and the dose to be used.

To bridge the gap between *in vitro* and *in vivo,* one approach is mathematical modeling which is used to support clinical predictions, providing richer data sets for model calibration, facilitating a model-based translation of *in vitro* cell assays to *in vivo* response (Lee et al., 2013; Checkley et al., 2015). Another strategy is the use of clinical trials in a dish (CTiD) which bridges preclinical testing and clinical trials allowing to test potential therapies for safety or efficacy on cells collected from a representative sample of human patients (Fermini et al., 2018; Seyhan, 2019).

Nowadays, for dental tissues, only P11–4 has been used in a clinical trial on children aged >5 years with visible active early caries on erupting permanent molars, showing enamel tissue regeneration and prevention of lesion progression (Alkilzy et al., 2018b). These results could change the clinical approach, avoiding additional loss of healthy tissue.

Regarding periodontal tissues, due to their complex composition, regenerative biomaterials should be capable to interact with hard and soft tissues at the same time (Elango et al., 2020). Many options have been studied *in vitro* with promising results that may lead to preclinical studies (Nagy et al., 2018). In this regard, it has to be considered that the success of the translation research from bench to bedside depends on the adoption of multidisciplinary strategies to overcome each of the many problems during the development process of SP therapy.

In normal conditions, PDL is under the influence of occlusal mechanical forces. However, these conditions cannot be completely achieved during *in vitro* or *ex vivo* tests. The *in vivo* model is the unique option that can imitate the occlusal state to support the functional regeneration design. Another challenge is the Sharpey's fiber regeneration and their insertion. The fibers absence nullify this important connection, defeating the tooth support and occlusal force (Liang et al., 2020).

Given this intricate relationship, few clinical studies using SP have shown regeneration. For instance, ABM/P-15, shows a favorable histologic healing, finding cementum, PDL, and alveolar bone on a previously calculus- and biofilm-contaminated zone, demonstrating its regenerative potential (Yukna et al., 2002).

In the case of SP used to promote bone healing and regeneration, most of them have only been evaluated *in vitro* or in preclinical animal studies. Among the SP reported for alveolar regeneration, PTH1-34 and P-15 have more extensive clinical use and are commercially available. PTH1-34 has therapeutic potential for oral bone lesions in periodontitis (Magda, 2010) and PepGen P-15 has been tested in human periodontal bone defects with favorable results (Pountos et al., 2016).

Regarding soft tissue, its healing and stability are essential to obtain predictive results from other regenerative procedures. Wound healing can be promoted by the application of SP to induce an accelerated wound healing, which should also benefit the clinical outcome of oral surgical procedures by assuring that the wound is more rapidly sealed off from the contaminated oral environment. This will lead to a more rapid connective tissue reorganization and contribute to a faster gain in wound strength, reducing the potential for scarring and scar tissue contraction (Villa et al., 2015).

Oral tissues work as an integrated unit and during their development, some proteins can participate in more than one tissue. This fact has led researchers to test the function of some SP designed for one tissue in another closely related one. In this regard, some promising SP could induce biomineralization in enamel, dentin, cementum, and alveolar bone, and other SP could function for regeneration of dentin-pulp and periodontal tissue complexes.

CONCLUDING REMARKS

SP used for oral tissue regeneration offer several advantages including increased specificity, small size, excellent safety, less immunogenicity, great stability, low risk of systemic toxicity, and low cost. Additionally, SP can be combined with scaffolds and cells, to induce cellular processes such as adhesion, proliferation, migration, differentiation, angiogenesis, and biomineralization that are required given the complex nature of oral tissues.

Even though most of the SP are still under investigation, some of them have been studied *in vitro* and *in vivo* with promising results that may lead to preclinical studies. There are SP that have

shown their efficacy in clinical trials such as P11-4 for enamel regeneration or caries prevention and ABM/P-15 for cementum, PDL, and alveolar bone on a previously calculus- and biofilm-contaminated zone. Also, some SP are commercially available such as PTH1-34 and PepGen P-15 which are used for bone defects treatment.

Finally, the use of SP could become a more accessible therapy for the treatment of damaged oral tissues, thus replacing the use of inert materials or therapies with recombinant proteins and growth factors that are currently highly used in practice dental. Nevertheless, well-designed clinical studies need to prove their value before they can be broadly used.

AUTHOR CONTRIBUTIONS

MB, LH, GM, AP-S, ER, US-B, and CV-M conceived and designed the content of this review; MB, LH, GM, MN, AP-S, ER, US-B, JG-P, MA-M, RR-P, and CV-M wrote de paper; all authors contributed to the final version of the paper and approved the submitted version.

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