Natural Antimicrobials in the Dental Pulp

ABSTRACT

Introduction: Like many tissues, the dental pulp is equipped with innate and adaptive immune responses, designed to defend against infection and limit its spread. The pulp’s innate immune response includes the synthesis and release of antimicrobial peptides by several dental pulp cell types. These naturally-occurring antimicrobial peptides have broad spectrum activity against bacteria, fungi and viruses. There is a resurgence of interest in the bioactivities of naturally-occurring antimicrobial peptides, largely driven by the need to develop alternatives to antibiotics. Methods: This narrative review focused on the general properties of antimicrobial peptides, providing an overview of their sources and actions within the dental pulp. Results: We summarized the relevance of antimicrobial peptides in defending the dental pulp, highlighting the potential for many of these antimicrobials to be modified or mimicked for prospective therapeutic use. Conclusion: Antimicrobial peptides and novel peptide-based therapeutics are particularly attractive as emerging treatments for polymicrobial infections, such as endodontic infections, because of their broad activity against a range of pathogens. (J Endod 2020;46:S2–S9.)

KEY WORDS

Antimicrobial peptides; dental pulp; host defense peptide; human; peptoid

The dental pulp has a remarkable ability to heal after insult or injury arising from infection or trauma. Although the healing and regenerative capacity of the dental pulp is well-recognized, the clearance of infection before pulpal tissue regeneration has been studied in much less detail. The dental pulp is equipped with an innate and adaptive immune response to defend against invading microorganisms. The innate immune response provides an effective and broad nonspecific first line of defense by combining the phagocytic capacity of cells such as neutrophils and macrophages with the release of factors such as antimicrobial peptides, enzymes, and other soluble mediators that have potent antimicrobial, chemotactic, and immunomodulatory actions. The intricacies of the adaptive immune system of the dental pulp, which provides an antigen-specific response via T and B cells, are beyond the scope of this review, but rather it is the secreted peptide components of the innate immune system with antimicrobial activity that are of interest.

Naturally occurring antimicrobial peptides present within the dental pulp contribute to the clearance of infection, immunomodulation, and the initiation of repair and regeneration. Therefore, the potential exists to exploit these peptides therapeutically to control infection and improve regenerative endodontic therapies. This review will focus on antimicrobial peptides by outlining some of their basic properties and providing an overview of their sources and actions within the dental pulp. We will also highlight the potential for many of these antimicrobials to be modified or mimicked for prospective therapeutic use. The appropriate use of antibiotics has become a critical issue in dentistry, and new guidelines have very recently been released by the American Dental Association. Because of the increasing threat of antimicrobial resistance and reports of greater antibiotic prescribing by dentists than the current guidelines recommend, it is an opportune time to examine the natural defenses of the dental pulp.

Naturally occurring antimicrobial peptides belong to a structurally diverse family of peptides with such important roles in defense that they have been evolutionarily conserved throughout the animal and plant kingdoms. The majority of mammalian antimicrobial peptides share common features such as cationicity and hydrophobicity (Table 1), with helical antimicrobial peptides often displaying amphipathicity (Fig. 1). The overall positive charge of antimicrobial peptides facilitates interaction with microbial membranes, which tend to have an overall negative charge. Mammalian cell membranes tend to be zwitterionic (no net charge), and therefore a less favorable electrostatic interaction explains the selectivity of antimicrobial peptides for microbial cell membranes. Despite the importance of cationicity for the initial
interaction with the microbial cell membrane, the hydrophobic and/or amphipathic nature of the peptide is important to facilitate its insertion into the lipid membrane. Within the oral cavity there are 3 important families of antimicrobial peptides: the defensins, the histatins, and the cathelicidins. The histatins are histidine rich helical peptides with potent antifungal activity, whereas the defensins contain 6 cysteine residues forming 3 intramolecular disulfide bridges, and the topology of disulfide bridge formation determines their classification. The α-defensins have disulfide bridges between cysteine residues 1-6, 2-4, and 3-5, whereas in the β-defensin family the disulfide bridging is between cysteine residues 1-5, 2-4, and 3-6. These intramolecular disulfide bridges stabilize the triple β-sheet tertiary structure of both the α- and β-defensin families. The only member of the cathelicidin family found in humans is LL-37, named in accordance with the single letter abbreviation for the first 2 residues in its sequence and the number of amino acids in its peptide chain. LL-37 lacks disulfide bridges and has a random coil conformation in hydrophilic environments; however, it adopts an α-helical structure in hydrophobic environments, which is typical of cell membranes. The adopted α-helix is amphipathic, consisting of a hydrophilic face, which contributes to the initial electrostatic interaction with the microbial membrane, and a hydrophobic face, which facilitates LL-37’s insertion into the membrane (Fig. 1). Antimicrobial peptides generally target intracellular targets. Although the focus of this review is on their antimicrobial activity, the defensins and LL-37 are widely known as host defense peptides, because in addition they have roles in immune modulation, angiogenesis, and wound healing.

**PEPTIDE SOURCES IN THE DENTAL PULP**

**Odontoblasts**

Because of their anatomic location, odontoblast cells are ideally located to provide the first line of defense for the dental pulp. Indeed, dentin itself is reported to sequester numerous peptides and proteins including adrenomedullin, which has antimicrobial activity. Although

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**TABLE 1 - Biophysical Characteristics of Antimicrobial Peptides Relevant to the Dental Pulp**

<table>
<thead>
<tr>
<th>Peptide name</th>
<th>Abbreviation</th>
<th>Peptide sequence</th>
<th>Peptide source in the dental pulp</th>
<th>No. of amino acids</th>
<th>Net charge</th>
<th>Hydrophobic ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human neutrophil peptide-1 (α-defensin 1)</td>
<td>HNP-1</td>
<td>ACRYRIPIACIAGERR YGTCIYQGIQRVLWACC</td>
<td>Neutrophil</td>
<td>30</td>
<td>+3</td>
<td>53</td>
</tr>
<tr>
<td>Human neutrophil peptide-2 (α-defensin 2)</td>
<td>HNP-2</td>
<td>ACRYRIPIACIAGERR YGTCIYQGIQRVLWACC</td>
<td>Neutrophil</td>
<td>29</td>
<td>+3</td>
<td>51</td>
</tr>
<tr>
<td>Human neutrophil peptide-3 (α-defensin 3)</td>
<td>HNP-3</td>
<td>ACRYRIPIACIAGERR YGTCIYQGIQRVLWACC</td>
<td>Neutrophil</td>
<td>30</td>
<td>+2</td>
<td>50</td>
</tr>
<tr>
<td>Human neutrophil peptide-4 (α-defensin 4)</td>
<td>HNP-4</td>
<td>ACRYRIPIACIAGERR YGTCIYQGIQRVLWACC</td>
<td>Neutrophil</td>
<td>33</td>
<td>+4</td>
<td>51</td>
</tr>
<tr>
<td>Human β-defensin 1</td>
<td>HBD-1</td>
<td>DHYNCVSSGGQCLYSAC PFTKIQCTCGYKACCK</td>
<td>Odontoblast</td>
<td>36</td>
<td>+4</td>
<td>36</td>
</tr>
<tr>
<td>Human β-defensin 2</td>
<td>HBD-2</td>
<td>GGDPYQGLQHSIAPVFC PRRKQIGTCTCGGLPGHKK</td>
<td>Odontoblast</td>
<td>41</td>
<td>+7</td>
<td>36</td>
</tr>
<tr>
<td>Human β-defensin 2</td>
<td>HBD-3</td>
<td>GIINTLKQYORVRQGRCAV LSCLPKQEEIQSCDRGRKCCRRK</td>
<td>Not determined</td>
<td>45</td>
<td>+11</td>
<td>33</td>
</tr>
<tr>
<td>Human β-defensin 2</td>
<td>HBD-4</td>
<td>EFERDRQGYSTACRKRKOR SQEYRGGPNTYA CCLRKWDSESLLNRTKP</td>
<td>Not determined</td>
<td>50</td>
<td>+6</td>
<td>32</td>
</tr>
<tr>
<td>LL-37</td>
<td>LL-37</td>
<td>LLGDFFRFKSEKIGKEF KRVQIKDFLRNL VPKRQDSEDLNLVRPTES</td>
<td>Neutrophil</td>
<td>37</td>
<td>+6</td>
<td>35</td>
</tr>
<tr>
<td>KE-18</td>
<td>KE-18</td>
<td>KEKFRVQIKDFLRNL</td>
<td>Truncated LL-37*</td>
<td>18</td>
<td>+4</td>
<td>41</td>
</tr>
<tr>
<td>EF-14</td>
<td>EF-14</td>
<td>EFKRQIKDFLR</td>
<td>Truncated LL-37*</td>
<td>14</td>
<td>+3</td>
<td>42</td>
</tr>
<tr>
<td>KR-12</td>
<td>KR-12</td>
<td>KRIVQIKDFLR</td>
<td>Truncated LL-37*</td>
<td>12</td>
<td>+5</td>
<td>41</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>NPY</td>
<td>YPSKPDQNGEDAPAE DMMARYRSAFLHYNLRTQRY</td>
<td>Nerves</td>
<td>36</td>
<td>+1</td>
<td>25</td>
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<tr>
<td>Substance P</td>
<td>SP</td>
<td>RPKQPFQGFLM</td>
<td>Nerves</td>
<td>11</td>
<td>+3</td>
<td>36</td>
</tr>
<tr>
<td>Neurokinin A</td>
<td>NKA</td>
<td>HKTDSVFLGM</td>
<td>Nerves</td>
<td>10</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide</td>
<td>CGRP</td>
<td>ACDATCVDTHRLAGLLS RSGGVKNNPVPTNGSKAF</td>
<td>Nerves</td>
<td>37</td>
<td>+4</td>
<td>43</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td>ADM</td>
<td>YRQSMNNFQGLRSFGC RFCYGTIDK KDNAPPKSKIIPQGY</td>
<td>Odontoblast/dentin</td>
<td>52</td>
<td>+6</td>
<td>28</td>
</tr>
</tbody>
</table>

Peptide charge and hydrophobic ratios were calculated by using the Calculation & Prediction function of the Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main.php). *Peptides KE-18, EF-14, and KR-12 are truncated sequences of LL-37 and are shown for comparison of their biophysical properties with the parent peptide. They have not been identified to date in the dental pulp.
odontoblast processes. Bacterial invasion of TRP channels on odontoblast cells and by the expression of transient receptor potential (TRP) channels on odontoblasts and odontoblast processes. The distinguishing epithelial barrier features of odontoblasts include their ability to act as sentinels of the dental pulp, detecting a wide variety of stimuli including chemical irritants, temperature changes, and bacteria. Chemical irritants and temperature changes are detected by the expression of transient receptor potential (TRP) channels on odontoblasts and odontoblast processes.

Bacterial invasion of the dental tubules accompanies the progression of dental caries, and as the infection reaches the dentin-pulp complex, the microflora changes from predominantly Gram-positive toward increased numbers of Gram-negative anaerobes. Therefore, it is appropriate that odontoblasts are equipped with toll-like receptors (TLRs) that detect both Gram-positive and Gram-negative bacteria as well as fungi, viruses, and endogenous damage signals via a range of additional TLRs. Activation of TLRs engages the effector arm of the innate immune system, recruiting in inflammatory cells such as neutrophils via a range of additional TLRs.

FIGURE 1 – Helical wheel projections showing amphipathicity of LL-37, KE-18, EF-14, and KR-12. Non-polar residues tend to be positioned on the hydrophobic face of the peptide, and the remaining residues contribute to its hydrophilic face. One letter abbreviations of amino acids are shown in squares, diamonds, and octagons. By default the aliphatic (non-polar) amino acids I, L, V, M are shown in squares, the acidic and polar amino acids D, E, N, Q, S, T are shown in diamonds, and the positively charged amino acids H, K, R are shown in octagons.

Recruited Inflammatory Cells: Neutrophils
The release of proinflammatory cytokines and chemokines by odontoblasts recruits inflammatory cells such as neutrophils. Neutrophils migrate from the bloodstream to the site of infection with remarkable efficiency, generally within 30 minutes, and their importance in defending the dental pulp cannot be overstated. The neutrophil contains primary azurophilic and secondary specific granules, which house a complex arsenal of antimicrobial peptides. The z-defensins, also known as human neutrophil peptides (HNP-1-4), are contained within the azurophilic granules, and LL-37 is found within the specific granules.

In studies on the antimicrobial activity of HNP-1, we reported good antimicrobial activity against Strepitococcus mutans, Staphylococcus aureus, Enterococcus faecalis, and Candida albicans in radial diffusion assays. However, HNP-1 and -2 did not fully inhibit growth of members of the Streptococcus miliaris group but rather showed only partial zones of clearing in radial diffusion assays. Further work by our research group showed antimicrobial activity of LL-37 against Gram-positive and Gram-negative bacteria and fungi in both planktonic and biofilm form. Using SYTOX green permeabilization assays, the antimicrobial activity was shown to be associated with membrane perturbation effects. LL-37 has also been shown to be efficacious against E. faecalis in planktonic form. Furthermore, when LL-37 was complexed with the glycosaminoglycan heparin, it retained antimicrobial activity against oral bacteria including S. mutans, Streptococcus sobrinus, Streptococcus salivarius, and Aggregatibacter actinomycetemcomitans, with decreased cytotoxic effects against dental pulp cells. Interestingly, LPS was shown to release LL-37 from its complex with heparin in a competitive manner, suggesting a mechanism for exploiting the controlled release of LL-37 in vivo.

Neutrophil antimicrobial peptides have both intracellular and extracellular killing functions. They act within the neutrophil to kill bacteria that have been phagocytosed. In addition, antimicrobial peptides can act extracellularly by 1 of 2 mechanisms, direct antimicrobial action against bacteria after neutrophil degranulation or via neutrophil extracellular traps (NETs). Neutrophil production of NETs has been shown to be stimulated by bacteria associated with endodontic infections. Thus, NETs encapsulate and kill bacteria, facilitated by the fact that they are decorated with antimicrobial peptides. In terms of immunomodulatory roles, LL-37 (and the defensins) can stabilize NETs against bacterial nucleic acid degradation.

Moreover, LL-37 has been shown to have a plethora of actions on oral fibroblasts, including significantly increased production of interleukin 8 (IL-8), IL-6, basic fibroblast growth factor, and hepatocyte growth factor. The combination of odontoblast secretion of HBD-1 and HBD-2, along with...
neutrophil production of HNP1-4 and LL-37, provides a robust odontoblast-neutrophil innate immune barrier to impending infection. The fact that antimicrobial peptides have broad antimicrobial activity against several species of microorganisms means that there is functional overlap or functional redundancy within the first-line innate immune response of the dental pulp, and this helps to maintain the security of the barrier. The immunomodulatory roles of antimicrobial peptides provide a further layer of complexity to their action, which may be apparent at lower concentrations than those required for direct antimicrobial activity.

**Fibroblasts**

Fibroblasts are the most abundant cell type in the dental pulp; however, they have been largely overlooked as important players in pulp defense. Like odontoblasts, fibroblasts express TRP channels for the detection of chemical/mechanical/thermal stimuli and TLRs for detection of microbial pathogens and endogenous damage signals. The presence of functional TRP channels and TLRs on pulp fibroblasts indicates that these cells participate in the pulpal response to environmental change and bacterial challenge. Furthermore, fibroblasts have recently been shown to have the ability to destroy cariogenic bacteria directly via complement proteins. After stimulation with lipoteichoic acid (LTA) to mimic infection with Gram-positive bacteria, pulp fibroblasts expressed all the complement molecules from C1 to C9. Complement activation was shown to lead to the formation of the membrane attack complex, with lytic effects against cariogenic bacteria, adding important antimicrobial and defensive roles to the repertoire of activities associated with the dental pulp fibroblast. Interestingly, fibroblasts have also been shown to express both neuropeptides and neuropeptide receptors. In particular, dental pulp fibroblasts have been shown to synthesize substance P and its receptor, the neurokinin-1 receptor. Furthermore, although pulp fibroblasts express the neuropeptide Y receptor Y1, they do not synthesize neuropeptide Y. Thus fibroblasts undoubtedly contribute to the pulpal neurogenic response outlined below by synthesizing selected neuropeptides and/or their cognate receptors, thereby adding an extra dimension to the neurogenic inflammatory response.

**Nerves**

TRP channels present on nerves signal pain to the central nervous system to warn of imminent danger to the dental pulp tissue. In addition to transmitting an afferent signal to the central nervous system, pulpal nerves also release neuropeptides through an axon reflex. Neuropeptides released peripherally contribute to inflammation in the local tissue environment, ie, the neurogenic inflammatory response. It has also been established that the nerve sprouting that accompanies the progression of caries is associated with increased levels of many neuropeptides within the dental pulp tissue including substance P, neurokinin A, vasoactive intestinal polypeptide, and neuropeptide Y. These locally released neuropeptides have many modulatory functions that are beyond the scope of this article but have been reviewed by us previously.

The physiochemical properties of neuropeptides, such as their net charge, hydrophobicity, and isoelectric point, resemble those of conventional antimicrobial peptides (Table 1). Our research group found that neuropeptides had antimicrobial activity against a range of human pathogens, including the oral pathogens S. mutans, E. faecalis, Lactobacillus acidophilus, and C. albicans. Because of the extensive innervation of healthy dental pulp tissue and the additional sprouting of nerves that occurs in response to caries, it is not unreasonable to suggest that neuropeptides released from dental nerves may be implicated in the fight against pulpal infection.

**Stem Cells**

To date there have been no reports regarding potential antimicrobial activity associated with dental pulp stem cells. However, stem cells from various sources have been shown to have direct antimicrobial activity, and the peptides and proteins associated tend to differ, depending on the stem cell niche. Bone marrow mesenchymal stem cells have antibacterial activity against both Escherichia coli and S. aureus, principally mediated by LL-37. The antibacterial activity of human umbilical cord blood mesenchymal stem cells against E. coli is mediated by β-defensin-2. In addition to classical antimicrobial peptides, oral mucosal lamina propria progenitor cells exert antibacterial activity against a range of pathogens via the secretion of osteoprotegerin and haptoglobin. The possibility that dental pulp stem cells produce antimicrobial factors is an area for further research study that we are currently exploring.

**PEPTIDE MIMETICS**

Because of the rise in antibiotic resistance, interest in exploiting antimicrobial peptides as potential therapeutics is growing. In addition to the de novo synthesis of antimicrobials based

### TABLE 2 - Antimicrobial Activity (MIC) of LL-37 and Truncated Mimetics KE-18, EF-14, and KR-12 against Oral Pathogens

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Peptide name</th>
<th>LL-37 MIC value µg/mL [µmol/L]</th>
<th>KE-18 MIC value µg/mL [µmol/L]</th>
<th>EF-14 MIC value µg/mL [µmol/L]</th>
<th>KR-12 MIC value µg/mL [µmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCTC 10449</td>
<td>48.29 [10.89]</td>
<td>2.66 [1.56]</td>
<td>82.04 [44.36]</td>
<td>5.97 [3.8]</td>
</tr>
<tr>
<td>F. nucleatum</td>
<td>ATCC 10562</td>
<td>4.4 [0.98]</td>
<td>6.6 [2.9]</td>
<td>101 [54.6]</td>
<td>5.4 [3.44]</td>
</tr>
<tr>
<td></td>
<td>NCTC 12697</td>
<td>45 [12]</td>
<td>9 [4.78]</td>
<td>100 [56.3]</td>
<td>6 [3.8]</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration.
on rational design approaches, much research has been devoted toward truncating or mimicking natural antimicrobial peptides to simplify their synthesis and retain their bioactivity.

**Mimetics of α- and β-Defensins**

In view of the conservation of the γ-core structural motif in disulfide bridge-containing antimicrobial peptides, this region is an attractive candidate for engineering functional truncated defensin analogues/mimetics. On the basis of this middle to c-terminal fragment (amino acids 14/15-30 of HNP-1) we previously designed and synthesized a range of truncated defensin analogues lacking disulfide bridges. Several of the truncated peptides displayed antimicrobial activity against a range of microorganisms, including S. aureus, S. mutans, and E. faecalis, indicating that disulfide bridges were not critical for HNP antimicrobial action. However, all the truncated mimetics tested were somewhat less active than the parent, HNP-1. Mimetics of HBs have also been developed, including a novel circular peptide, combining features of 2 human β-defensins, with retention of antimicrobial activity.

**Mimetics of LL-37**

LL-37 adopts an α-helical conformation, particularly in the vicinity of the plasma membrane. The biological activity of LL-37 resides within the mid-region of the molecule, and truncation to mid-region fragments has resulted in peptides of variable efficacy against S. aureus, E. coli, and C. albicans. In additional (unpublished) work by us (Table 2), KE-18 and KR-12 were shown to display improved efficacy (determined by radial diffusion assay) compared with the parent peptide against selected oral pathogens, whereas EF-14 was antimicrobial only at very high peptide concentrations.

In addition to direct antimicrobial activity, the immunomodulatory roles of host defense peptides and their mimetics are also of interest. The ability of peptides to bind LPS and/or LTA is important in dampening TLR responses, because LL-37 has been shown to effectively neutralize LPS. The peptide mimetics KE-18 and KR-12 were shown to bind E. coli LPS in vitro with similar efficacy to the parent molecule, LL-37. Moreover, the S. aureus LTA binding efficacy of KE-18 was significantly greater than that of LL-37. Further studies have shown that KE-18 has significantly greater binding efficacy with Porphyromonas gingivalis LPS than the parent peptide, LL-37 (Fig. 2). These results highlight the truncated mimetic KE-18 as a potential modulator of the immune response and a direct antimicrobial agent in vitro.

**UNNATURAL PEPTIDE MIMETICS**

A potential disadvantage of peptide-based therapeutics is the fact that they are susceptible to degradation by peptidases present in the inflammatory milieu. Truncation may reduce the number of susceptible proteolytic sites within a peptide, but unless the mimetic is substantially different from the parent molecule (in which case the biological activity may be altered), it is likely to retain at least some proteolytic cleavage sites. Many strategies have been adopted to stabilize peptides with variable success, including the use of unnatural amino acids, peptide stapling, cyclization, lipidation, and PEGylation.

**Peptoids**

One strategy that has recently come to the fore is backbone modification, through the use of N-substituted glycine residues, to make peptide mimetics known as peptoids. This results in the side chain groups being located on the nitrogen rather than the alpha carbon atom (Fig. 3). Peptoids have inherent stability to peptidases and have been shown to retain potent antimicrobial activity. They can be synthesized de novo to generate novel antimicrobials with many of the generic features of antimicrobial peptides or synthesized to mimic specific antimicrobial peptides of interest. We previously designed and synthesized a de novo family of peptoids with alpha-helical secondary structure and potent antimicrobial activity against biofilms. Whether such peptoids will be translated into therapeutic interventions remains to be determined.

**DISCUSSION**

The dental pulp is a unique tissue containing specialized resident cells, stem cells, and infiltrating inflammatory/immune cells, all of which contribute to the pulp’s defense strategy. In addition, the extensive innervation of the dental pulp facilitates not only the detection of painful stimuli but also a neurogenic inflammatory response, which results in the local release of neuropeptides, some of which have direct antimicrobial properties. Together the cells (resident and recruited) and the nerves of the dental pulp contribute to defense against infection and to the clearance of infection when the defensive barrier has been breached.

Although the central dogma that infection delays subsequent repair and regeneration is relevant to the dental pulp, relatively little attention has been paid to the pulp’s natural antimicrobial capacity, in comparison with the volume of literature on its regenerative capacity. Moreover, it is worth considering that many naturally occurring antimicrobial peptides have immunomodulatory properties and are therefore often referred to as host defense peptides to emphasize their roles beyond antimicrobial action. These immunomodulatory properties can include LPS-LTA-binding ability and subsequent dampening of TLR-mediated proinflammatory responses. Indeed, the multifunctionality of antimicrobial peptides in the clearance of infection and in modulating inflammation points to their therapeutic usefulness in endodontic therapies. Although data are limited on the regenerative effects of antimicrobial peptides, LL-37 has been shown to be biocompatible with dental pulp stem cells in vitro and has been suggested as a possible adjunct for their enhanced proliferation and differentiation.

Emerging interest in the research field of natural antimicrobial and immunomodulatory peptides can only enlighten the future pathway for successful pulp regenerative strategies. Customized peptide hydrogels could be engineered to contain antimicrobial peptides with the potential to have direct antimicrobial action against endodontic pathogens. Thus the hydrogel scaffold could contribute to
resolving/limiting the infection before pulpal regeneration.

CONCLUSION
There are exciting clinical developments in maintaining the vitality of the dental pulp, and future therapeutic interventions should fully consider the importance of preserving both the natural antimicrobials of the pulp as well as its regenerative capacity. Because of their broad activity against a range of pathogens, novel peptide-based therapeutics are particularly attractive for efficacy against polymicrobial infections such as endodontic infections.

ACKNOWLEDGMENTS
The authors deny any conflicts of interest related to this study.

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