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Research review paper

Antimicrobial peptide-based treatment for endodontic infections — Biotechnological innovation in endodontics

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ABSTRACT

The presence/persistence of microorganisms in the pulp and periapical area corresponds to the maintenance of an exacerbated immune response that leads to the start of periradicular bone resorption and its perpetuation. In endodontic treatment, the available intracanal medications do not have all the desirable properties in the context of endodontic infection and apical periodontitis; they need to include not only strong antimicrobial performance but also an immunomodulatory and reparative activity, without host damage. In addition, there are various levels of resistance to root canal medications. Thus, antimicrobial agents that effectively eliminate resistant species in root canals could potentially improve endodontic treatment. In the emergence of new therapies, an increasing number of studies on antimicrobial peptides (AMPs) have been seen over the past few years. AMPs are defense biomolecules produced in response to infection, and they have a wide spectrum of action against many oral microorganisms. There are some studies that correlate peptides and oral infections, including oral peptides, neuropeptides, and bacterial, fish, bovine and synthetic peptides. So far, there are around 120 published studies correlating endodontic microbiota with AMPs but, according to our knowledge, there are no registered patents in the American patent database. There are a considerable number of AMPs that exhibit excellent antimicrobial activity against endodontic microbiota at a small inhibitory concentration and modulate an exacerbated immune response, down-regulating bone resorption. All these reasons indicate the antimicrobial peptide-based endodontic treatment as an emerging and promising option.

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Introduction

Carious lesions are the main cause of pulp infection, and their progression is motivated by the virulence and proliferation of microorganisms (Siqueira and Rocas, 2008, Zero et al., 2011a). These microorganisms initiate the pulpitis process, characterized by neurogenic inflammation and much pain (Jancso et al., 1967), which needs endodontic treatment. Failure in endodontic therapy may be due to the presence and persistence of pathogenic microorganisms that resist disinfection procedures in the root canal system (RCS). These pathogens may start or maintain an immune-inflammatory process that leads to local bone resorption (Figdor, 2004). In addition, they may evade chemical and mechanical procedures and infiltrate into dentinal tubules (Figdor et al., 2003). Traditional intracanal dressing does not have all the desirable properties to eliminate resistant microorganisms and promote tissue repair. In this situation, pathogens and a chronic immune-inflammatory response in persistent endodontic infections are possible targets for the development and introduction of new therapies in endodontics, including biotools as antimicrobial peptides (AMPs).

The AMPs are endogenous biomolecules mainly produced early in response to infection in order to maintain the health and disease relationship between the host and pathogen (Gorr and Abdolhosseini, 2011; Silva et al., 2011). These biomolecules may act in different manners, interacting with the surface of microbial membranes or acting inside the target cell, presenting a broad spectrum of activity (Zasloff, 2002). The low antimicrobial concentration and tissue repair capability of AMPs (Silva et al., 2012a) highlight their potential to act as intracanal dressing in cases of endodontic failure due to the multiple mechanisms described.

Studies on AMPs and indeed their use in medical and pharmacological areas are more advanced than in dentistry. All these advances have indicated that these compounds perform well against some endodontic microorganisms, besides modulating the immune-inflammatory response. This review focuses on demonstrating the potential use of AMPs as intracanal dressing and the benefits of their application in the outcome of endodontic therapy. Here we will shed some light on how these biomolecules may improve endodontic approaches and focus on studies and patents in the area of endodontic innovation. We will examine the commercial availability of dental products, besides clarifying all the variables in the application and benefits from the use of AMPs in endodontics.

Infectious processes of the endodontic environment

Pulpal and periapical infections

Carious lesions are the most common cause of pulp infections, and the progression of this disease is driven by factors such as the virulence and proliferation of microorganisms (Siqueira and Rocas, 2008, Zero et al., 2011b). The dental pulp is an immunocompetent tissue that in many cases can reestablish a healthy status once a pathogen is removed (Stashenko et al., 1998; Torabinejad et al., 1985). Pulp inflammation begins before direct contact between pathogens and pulp tissue (Zero et al., 2011b). Inflammatory pulp cells react promptly to the initial stage of caries, starting a chronic inflammation in the subodontoblastic area. Mononuclear cells represent the first cell line of pulp defense (Zero et al., 2011b). In this way, carious lesion progression leads to an increase in the number of inflammatory cells, and neutrophils emerge in this infectious environment. During pulp inflammatory/immune response, mineralized and inextensible dentin walls prevent the development of edema, which compromises blood circulation and isolates the necrotic pulp from body defense responses, enabling infection to be perpetuated (Baumgartner and Falkler, 1991). Necrosis migrates apically and can gradually reach the whole pulp (Ricucci and Siqueira, 2010). After pulp necrosis, the infection evolves to the periapical region. At first, this process can trigger a non-specific inflammatory reaction followed by a specific immune response as well as bone destruction in the periapical area (Silva et al., 2012b; Stashenko et al., 1998; Torabinejad et al., 1985) (Fig. 1).

The selection of microorganisms in the necrotic pulp over time involves the conditions of low oxygen-reduction potential, reduced oxygen consumption and nutrient availability, increasing cellular degradation and also the presence of bacterial sub-products (Siqueira, 2002). The microorganisms that adapt to these conditions can colonize the RCS during or after endodontic therapy and cause persistent pain by impairing the sensitivity of antibiotics, inhibiting neutrophil and mononuclear phagocyte chemotaxis. These pathogens can also produce enzymes (hyaluronidase, collagenase, condroitinase, acid phosphatase) and endotoxins related to direct and indirect tissue damage. In addition, the root canal infection profile tends to be anaerobic and is preceded by aerobic infections or by a compromised blood supply (Farber and Seltzer, 1988; Fouad et al., 2002; Siqueira, 2002).

Several microorganisms of infected root canals are capable of surviving long periods of scarce oxygen and nutrients. In addition, these microorganisms resist environmental changes and reach sufficient numbers to cause perpetuation of infection and periapical lesion, once they overcome host defenses (Siqueira and Rocas, 2008). Evidence indicates that the failure of endodontic treatment may be motivated by the presence/persistence of such pathogens, which are resistant to disinfection procedures in the apical portion (Gajan et al., 2009). Samples from patients submitted to endodontic retreatment revealed the prevalence of *Enterococcus faecalis*, *Pseudoramibacter alactolyticus*, *Propionibacterium propionicum*, *Filifactor alocis* and *Dialister pneumosintes* by means of PCR (Siqueira and Rocas, 2004). Another study involving culture and molecular techniques characterized the following species: *Candida albicans*, *E. faecalis*, *Propionibacterium acnes*, *P. propionicum*, *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Anaerococcus prevotii*, *Eggerthella lenta*, *Gemella morbillorum*, *Parvimonas micra*, *P. alactolyticus*, *Streptococcus anginosus* and *Streptococcus mitis* (Siqueira and Rocas, 2009). Thus, the failure of endodontic treatment has often been motivated by the presence of *Enterococcus* and *Streptococcus* species (Gomes et al., 2004). Results of many studies that identified microorganisms from periapical lesions are demonstrated in Table 1.

Once microorganisms migrate to the periapical tissue, they are surrounded by inflammatory tissue, polymorphonuclear neutrophils or epithelial plugs, representing an immune-inflammatory response against the evolution of infection (Fig. 1). The inflammatory exudate presents a large number of immunocompetent cells (macrophages; CD4+, CD8+ and CD30+ lymphocytes; natural killer cells; mast cells; and eosinophils), involved in innate immune response. In this way, cells are able to phagocyte microorganisms and dead cells (Teixeira-Salum et al., 2010b).

The maintenance of an adaptive immune response in the periapical area culminates in the osteoimmunologic events that lead to periradicular bone resorption (Teixeira-Salum et al., 2010a). Bone resorption comprises osteoclastogenesis and osteoclast activity. Osteoclastogenesis stars with the osteoclast precursor (monocyte and macrophage lineages) differentiating into multinucleated osteoclast mediated by the receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is produced by osteoclasts, bone stromal cells and B and T activated lymphocytes and is involved in physiologic and pathologic osteoclastogenesis and osteoclast activity (Fukada et al., 2009). The RANKL receptor, RANK protein, is located on the cellular surface of osteoclast precursor cells and, when activated by its ligand, promotes the activation of nuclear factor kappa B (NF-κB), required for osteoclast differentiation and maturation (Wittrant et al., 2008). The mature osteoclast secretes protons and lytic enzymes in the bone resorption vesicle formed between the osteoclast and bone tissue. Cathepsin K and tartrate-resistant acid phosphatase (TRAP) are important enzymes in these processes, responsible for collagen matrices and bone degradation (Taubman and Kawai, 2001).