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## Perspective

# Herpesviral-bacterial synergy in the pathogenesis of apical periodontitis: New insights and future perspectives

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Apical periodontitis (AP) represents a persistent inflammatory reaction within periapical tissues of teeth devoid of vital pulp.<sup>1</sup> Although it is considered as a multifactorial disease, in most of the cases it develops from the exposure of the vital pulp to different oral microbiota as a result of dental caries, accidental trauma or iatrogenic causes.<sup>1</sup> Healthy dental pulp is a sterile environment, and, hypothetically, any microbe from the oral cavity may cause endodontic infection with subsequent destruction of tooth supporting tissues in the periapical region.<sup>1</sup>

The presence of herpesviral DNA in samples of periapical lesions was identified for the first time in 2003, suggesting its potential implication in the pathogenesis of AP. Namely, Slots and co-workers<sup>2</sup> proposed a herpesviral-bacterial hypothesis by which herpesviruses may cause the destruction of periapical tissues as a result of direct cytopathogenic effects of different cell types in periapical region. They also claimed that herpesviruses may impair the local host defense and enhance aggressiveness of resident bacterial pathogens by several indirect mechanisms including inhibition of the major histocompatibility complex class I and II expression on the surface of macrophages, induction of pro-inflammatory cytokines production, evasion of apoptosis,

etc.<sup>2</sup> Although two previous studies<sup>3,4</sup> have reported the presence of herpesviral–bacterial co-infection in AP samples, other published investigations in the past two decades were rather conflicting. Noteworthy, the pooled data of eligible studies presented in a recent meta-analyses did not reveal a significantly more frequent presence of herpesviral infection in AP cases versus healthy controls,<sup>5</sup> nor between symptomatic versus asymptomatic AP cases.<sup>6</sup> Taken together, except the mere presence of herpesviral DNA and/or RNA in the investigated AP samples, there was no direct evidence of herpesviral involvement in the pathogenesis of this tooth disease.

Specific molecular mechanisms by which herpesviruses alone, or synergistically in co-infection with bacteria of endodontic origin may cause or exacerbate periapical inflammatory processes remained under-investigated until recent groundbreaking findings.<sup>7–10</sup> The first important result was presented by a group of Japanese scientists who revealed that n-butyric acid produced by *Porphyromonas endodontalis* (PE) reactivated latent *Epstein–Barr virus* (EBV) infection in an *in vitro* model.<sup>7</sup> The authors found that the promoter region of BamHI fragment Z leftward open reading frame 1 (BZLF-1) and BamHI fragment Z EB replication activator (ZEBRA) protein were expressed by Daudi cells (i.e. a Burkitt lymphoma cell line positive for the presence of EBV), in a dose-dependent manner after the treatment with PE culture supernatants, pointing to the induction of virus reactivation. In parallel, they also analyzed their patients' samples of periapical lesions and

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detected *P. endodontalis* and BZLF-1.<sup>7</sup> In their next study on the same type of cells, the authors strengthened the idea of herpesviral-bacterial synergy in AP by showing that *Fusobacterium nucleatum*, another periodontopathic bacterium, also induced the expression of BZLF-1 mRNA and ZEBRA protein, two indicators of EBV reactivation.<sup>8</sup> These investigations are highly important because they clearly put forward the herpesviral-bacterial synergy in apical periodontitis pathogenesis.

A pioneering investigation was conducted by Serbian scientists who proposed a model of EBV induced bone resorption in AP via increased production of reactive oxygen species (ROS) and bone resorption regulators. For the first time a research group presented and examined the mechanisms of EBV involvement in alveolar bone resorption in AP.<sup>9,10</sup> Namely, authors hypothesized that EBV infection in AP samples may contribute to increased ROS production and consequent overexpression of receptor activator of nuclear factor kappa B (NF- $\kappa$ B) ligand (RANKL) which, after binding to its cellular receptor RANK, leads to differentiation of precursor cells into osteoclast and increased bone resorption.<sup>9,10</sup>

Future goals should be directed toward substantiating these findings in AP experimental animal models. This is a very challenging task due to technical difficulties and limitations encountered in the process of creation of experimental animals carriers of human viruses. At present, such models are still inexistant for some herpesviruses.

Additionally, the use of appropriate antiviral therapy in terms of dosage, approaches to drug administration and the most suitable forms of drugs, should be investigated in herpesvirus infected AP cases. Presently, there are no clinical studies on antiviral therapy application in the treatment of AP cases and they are very much needed.

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