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Cell responses to cariogenic microorganisms and dental resin materials—Crosstalk at the dentin-pulp interface?

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ABSTRACT

Objective. Resin monomers released from unpolymerized dental adhesives or composites and bacterial products like lipopolysaccharide (LPS) or lipoteichoic (LTA) are simultaneously present in specific applications following treatment of deep caries lesions. This review is focused on evidence concerning cell responses as a result of the interactions between adaptive mechanisms activated by resin monomers and signaling pathways of the immune response triggered by LPS or LTA originating from cariogenic microorganisms.

Methods. Current understanding of dental caries progression and pathways in eukaryotic cells in response to LPS stimulation in a clinical situation as well as cell reactions to oxidative stress caused by resin monomers is analyzed based on publications available through online databases.

Results. LPS and LTA activate the redox-sensitive transcription factor NF-κB as a major regulator in immunocompetent dental pulp cells. Cell reactions to LPS/LTA associated with oxidative stress are downregulated by the redox-sensitive transcription factor Nrf2. Thus, activation of Nrf2 through resin monomer-induced oxidative stress due to the increased formation of reactive oxygen species (ROS) could be a molecular mechanism underlying the inhibition of LPS-stimulated responses such as the release of pro- or anti-inflammatory cytokines. Likewise, crosslinking of NF-κB and Nrf2-regulated biocompatibility pathways regulates cell death induced by the interaction of LPS and resin monomers.

Significance. A multidimensional scenario through independent but linked NF-κB- and Nrf2-regulated pathways is activated in the clinical situation of caries treatment. Unfavorable or beneficial consequences strictly depend on a wide range of combinations and concentrations of bacterial products and resin monomers.

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Contents

1. Introduction

Current concepts relating to dental restorative materials exclusively used to maintain structure and function of teeth are presently undergoing drastic change. An increasing number of restorative dental materials actively interfere with regulatory pathways stimulating regenerative processes in periodontal and pulp tissues. Materials like tricalcium silicate cements recommended for vital pulp therapy were shown to induce odontogenic differentiation in dental pulp stem cells (DPSCs) leading to dental hard tissue formation. These materials were considered bioactive because of their regenerative properties [1,2]. Yet, insight into the cellular mechanisms of these processes is very limited compared to the latest progress in research on the bioactivity or biocompatibility of restorative dental materials [3]. Moreover, the characterization of substances as bioactive or biocompatible encompasses a much broader range of dental biomaterials than much of the dental community has indicated so far. Dental materials, or their compounds, are considered bioactive if they induce changes in cellular homeostasis as a consequence of their interaction with cellular receptors or regulatory proteins, and subsequently activate pathways leading to specific adaptive cell responses. In this respect, biocompatibility is not a property of a material but instead describes the complex interplay between the characteristics of a material and a specific target tissue. This makes it essential for biocompatibility to be considered when referring to a specific application since different materials interfere with various biological systems in a variety of ways [4].

This review focuses on cellular mechanisms activated by materials present in cavitated carious lesions. In particular, we analyzed the interaction between the specific effects initiated by lipopolysaccharide (LPS) released from cariogenic microorganisms and the influence of resin monomers as compounds of long lasting dental restorations. We first concisely describe the process of dental caries progression to explain the pathways in eukaryotic cells in response to LPS or LTA (lipoteichoic acid) stimulation in a clinical situation. These pathogen-associated molecular patterns (PAMP) activate the redox-sensitive transcription factor NF-κB, which in turn is part of the regulation of immune responses of various cell types in dental pulp tissues like the release of pro- or anti-inflammatory cytokines. There is also evidence that reactions of immune cells in response to NF-κB are controlled by the transcription factor Nrf2 (nuclear factor erythroid 2 [NF-E2]-related factor 2). It seems that the activation of NF-κB and Nrf2 pathways by LPS critically depends on oxidative stress [5,6]. Likewise, oxidative stress as a result of the increased formation of reactive oxygen species (ROS) is produced in cells exposed to dental resin monomers like TEGDMA (triethyleneglycol dimethacrylate) or HEMA (2-hydroxyethyl methacrylate). Subsequently, the expression of Nrf2 and Nrf2-regulated enzymatic antioxidants is increased as an adaptive cell response [7]. In addition, we consider various cellular pathways activated or influenced by ROS in monomer-exposed cells. Finally, we discuss the interaction of LPS- and monomer-stimulated cell responses based on crosslinks between NF-κB and Nrf2-related biocompatibility pathways. These cell reactions reflect the complex and multidimensional scenarios crucial in the clinical management of carious lesions.

2. Dental caries and the activity of cariogenic organisms

Dental caries is a multifactorial infectious disease of dental hard tissue caused by a complex biofilm of acidogenic and aciduric pathogenic microorganisms, among other species, which stimulate demineralization processes of enamel and dentin. Although the etiology of dental caries was initially related to the activity of *Streptococcus mutans* as a keystone pathogen, the current paradigm favors the collective interplay of a complex microbiome rather than the activity of a singular species [8,9]. The multi-species community of cariogenic Gram-positive bacteria including mutans and non-mutans streptococci, actinomyces, lactobacilli, or bifidobacteria species of supposedly predominantely active organisms are accompanied by Gram-negative species like *Prevotella*, *Porphyromonas* or *Fusobacterium species* in a dynamic biofilm [9,10]. Differential accumulation of acids through the fermentation of sugars and nutrition by a lively ecosystem of cariogenic bacteria produces an acidic environment which is considered a primary factor in changing the diversity of the microbial community [9,11]. The continuous imbalance