Inflammation and Regeneration in the Dentin-Pulp Complex: A Double-edged Sword

Paul R. Cooper, BSc, Michelle J. Holder, BSc, and Anthony J. Smith, BSc, PbD

Abstract

Dental tissue infection and disease result in acute and chronic activation of the innate immune response, which is mediated by molecular and cellular signaling. Different cell types within the dentin-pulp complex are able to detect invading bacteria at all stages of the infection. Indeed, at relatively early disease stages, odontoblasts will respond to bacterial components, and as the disease progresses, core pulp cells including fibroblasts, stem cells, endothelial cells, and immune cells will become involved. Pattern recognition receptors, such as Toll-like receptors expressed on these cell types, are responsible for detecting bacterial components, and their ligand binding leads to the activation of the nuclear factor-kappa B and p38 mitogen-activated protein (MAP) kinase intracellular signaling cascades. Subsequent nuclear translocation of the transcription factor subunits from these pathways will lead to proinflammatory mediator expression, including increases in cytokines and chemokines, which trigger host cellular defense mechanisms. The complex molecular signaling will result in the recruitment of immune system cells targeted at combating the invading microbes; however, the trafficking and antibacterial activity of these cells can lead to collateral tissue damage. Recent evidence suggests that if inflammation is resolved relatively low levels of proinflammatory mediators may promote tissue repair, whereas if chronic inflammation ensues repair mechanisms become inhibited. Thus, the effects of mediators are temporal context dependent. Although containment and removal of the infection are keys to enable dental tissue repair, it is feasible that the development of antiinflammatory and immunomodulatory approaches, based on molecular, epigenetic, and photobiomodulatory technologies, may also be beneficial for future endodontic treatments. (J Endod 2014;40:546–551)

Key Words

Dentin, enamel, epigenetic, extracellular matrix, histone deacetylase inhibitors, interleukins, low-level light therapy, migration, pulp, reactive oxygen species

Cellular and molecular responses occur in the pulp in response to dental caries and trauma, and these events can manifest into inflammatory and/or regenerative events at the tissue and cellular levels. The pulp, like any other injured tissue in the body, will initially mount a defense response in an attempt to remove the infection and enable the wound healing response to prevail (1, 2). Clearly, the tooth represents a specialized environment with low compliance with a limited tissue swelling capacity and has a relatively poor lymphatic drainage system. Subsequently, an infection can result in severe discomfort for the patient in the form of a “toothache.” As part of the tooth’s defense against invading microbes, cells within the pulp release molecular mediators, such as cytokines and chemokines, which lead to the recruitment of inflammatory and immune cells to the site of infection and injury. Subsequently, these cells attempt to eliminate the invading bacteria and remove any resulting host tissue debris (3). The source of the molecular mediators of the inflammatory response is somewhat dependent on the stage of infection because at a relatively early stage of disease it is the odontoblasts that will be involved in the initial environmental sensing and invoking of the innate immune response, whereas at later stages of the disease pulp fibroblasts, endothelial cells, pulp stem cells, and tissue resident immune cells will detect and respond to the bacteria (3–6). Notably, evidence now suggests that regenerative events may be enabled in relatively slowly progressing or arrested caries, whereas these events may be abrogated in rapidly progressing caries in which chronic inflammation may ensue (3).

Infection and Inflammation in the Tooth

Cariogenic bacterial biofilm composition evolves and adapts as disease progresses through the enamel, dentin, and pulp; in particular, as the environment becomes more anaerobic, the polymicrobial infections become increasingly complex and have a high bacterial diversity (7). Notably, pulp cell and tissue death occurs beneath rapidly progressing carious lesions as the bacteria release toxins and compete for nutrients within the microenvironment. The odontoblasts that are located at the periphery of the pulp are the first cells to encounter the invading bacteria. Several recent studies have shown that they are immunocompetent cells capable of orchestrating an inflammatory response. Indeed, they are able to detect infection within dentin at a relatively early stage because of the diffusion of bacterial components and metabolites within the tubules. In response, they are known to release autocrine and paracrine signaling factors such as chemokines and cytokines as well as antimicrobial peptides targeted at killing the invading microbes (5, 6). The odontoblasts and, subsequently, the pulp fibroblasts, endothelial cells, and stem cells detect bacterial components via pattern recognition receptors (PRRs). Arguably the best characterized family of PRRs is the Toll-like receptors (TLRs), which recognize a range of pathogen-associated molecular patterns. There are 11 members of the TLR family thus far identified, and they are
expressed on cell membranes and intracellularly on endosomes. Their expression is not limited to immune cells because they are also detected on structural cells from many tissues in the body. Dentally relevant examples of pathogen-associated molecular patterns that are detected by TLRs include lipoteichoic acids by TLR2, lipopolysaccharides (LPSs) by TLR4, flagellin by TLR5, and bacterial DNA/RNA by TLR9 (8, 9). TLRs 1–6 and 9 have been shown to be present in pulp tissue and are expressed on odontoblasts, fibroblasts, pulp stem cells, and endothelial cells (4, 5, 10–13). Other PRRs have been shown to be present within the pulp and the nucleotide-binding oligomerization domain (NOD) 1 and 2 proteins are expressed intracellularly in pulp-derived cells. Both NOD 1 and 2 have been detected in odontoblasts, pulp fibroblasts, and endothelial cells, and NOD 1 has been shown to be up-regulated during pulp inflammation. In addition, the Nod-like receptor family member pyrin domain containing 3, also known as the inflammasome, has recently been shown to be present on odontoblasts and pulp vascular endothelial cells (14–18).

Bacterial ligand binding to TLRs, NODs, and the inflammasome results in the activation of key intracellular signaling pathways involving nuclear factor-kappa B (NF-κB) and p38 mitogen-activated protein (MAP) kinase, which result in the elaboration of extracellular cytokine and chemokine secretion (10–13). These secreted molecules are relatively small but highly potent autocrine and paracrine mediators of inflammation and have been shown to be released by odontoblasts, pulpal fibroblasts, stem cells, and tissue-resident immune cells. They generate an intricate signaling network, and binding to their receptors present on several cell types can result in amplification of the inflammatory response within the tissue. Key and well-characterized cytokines and chemokines include interleukin (IL)-1α, IL-1β, tumor necrosis factor alpha (TNF-α), IL-4, IL-6, IL-8, and IL-10. In addition, there are many more inflammatory molecules mediators (eg, $\text{S100}$ proteins), many of which are shown as being up-regulated in diseased pulp tissue (19–23). Indeed, our preliminary studies (Fig. 1A–C), which aim to develop an in vitro model system, are in good agreement with these previous reports. Our findings show that proinflammatory mediators involved in pulp and cariogenic disease including Streptococcus mutans, TNF-α, and IL-1β along with the bacterial component LPS are able to stimulate activation of the NF-κB pathway, likely via the expressed TLRs, in primary dental pulp cells (24) within 1 hour. This activated intracellular signaling cascade subsequently results in increased cytokine and chemokine gene expression at 4 hours, which also appears to be chronically stimulated at later 24-hour time points in cultures (data not shown). Clearly, such cellular and molecular activity will result in the generation of complex autocrine and paracrine signaling, which are unlikely to be resolved until the bacterial infection is removed.

In addition to the cellular expression of these molecules, the demineralization of dentin by bacterial acids during the carious disease process may also add to cytokine levels because these molecules are known to be present within the dentin matrix and released in an acidic environment (25, 26). The milieu of the signaling molecules released into the extracellular environment will also result in the generation of chemotactic gradients for focused recruitment and activation of immune system cells from the vasculature and surrounding tissue. Immune system cells are also known to be resident in healthy pulp where they are proposed to play a sentinel role; however, as a result of disease, T and B lymphocytes, plasma cells, neutrophils, and macrophages are all significantly increased in levels at the site of the diseased lesion (27–29). The migration of the immune cells through the pulpal tissue and their antimicrobial activity can cause significant collateral host tissue damage. Notably, during the process of immune cell chemotaxis, proteases, such as metalloproteinases, are released, and to combat bacteria, immune cells release reactive oxygen species (ROS) and other potent enzymes, which can cause significant pulpal cell and tissue collateral damage. The damage signals released by the host’s dying cells can lead to further exacerbation of the proinflammatory response (5, 30, 31).

**Molecular and Cellular Events Underpinning Dental Tissue Regeneration**

Tertiary dentinogenic events can occur in response to tissue injury, and data indicate that infection and inflammation strongly impact on the repair processes within the dental tissue. Reactionary dentinogenesis occurs in response to a relatively mild dental tissue injury, such as during the earlier stages of dental caries, and odontoblasts lining the pulp chamber and root canal survive and up-regulate their synthetic and secretory activity. However, the process of reparative dentinogenesis is relatively more complex and occurs in response to a greater intensity of tissue injury, such as a more rapidly progressing carious injury, which initially results in odontoblast death and dentin loss beneath the lesion and may lead to pulp exposure. Subsequently, if conditions are conducive to repair, stem/progenitor cells are recruited to the site of injury where they differentiate to form new odontoblast-like cells that secrete tertiary dentin, resulting in dentin bridge formation above the exposed pulp (32). In addition to restoration of the hard physical structure of the tooth, the soft pulpal tissue architecture will also regenerate beneath the lesion, and angiogenic and neurogenic repair will occur (33–35). Key growth factors involved in signaling pulpal angiogenic and neurogenic events include vascular endothelial growth factor, fibroblast growth factor-2, nerve growth factor (NGF), brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor, and in addition several proinflammatory cytokines exhibit multifunctionality and can also contribute to the signaling of these repair processes (36–47). Clearly, the roles of these cytokines at any given point within the disease and repair process may be context and concentration dependent. Multiple sources, including local cell secretion and the hard and soft extracellular matrices (ECMs), can provide and deliver signaling molecules necessary for repair to the site of injury. Interestingly, many of these growth factors and cytokines in their free form have relatively short half-lives, usually in the order of minutes or seconds (48), and therefore their protected release from the ECM, where they have been sequestered, is likely essential to signaling repair. Notably, it is the odontoblasts that have secreted these signaling molecules into the dentin ECM, where they provide a “fossilized” reservoir of growth factors and cytokines, for future release when required (49–52). Several studies have now documented the importance of the “damage” signals released from dentin ECM not only by carious acids but also by restorative materials, including calcium hydroxide, mineral trioxide aggregate (MTA), and EDTA, which not only promote tertiary dentinogenic events but also the associated repair processes of angiogenesis and neurogenesis (53–56).

Clearly, the molecular signaling necessary is relatively simple in reactionary compared with reparative dentinogenesis (57). Indeed, during reactionary dentinogenesis, the locally released dentin ECM molecules, combined with bacterial components, and relatively low-level cytokines generated by resident cells will likely result in direct up-regulation of odontoblast dentin synthetic and secretory activities. However, in reparative dentinogenesis, after resolution or control of the infection, the signaling molecules derived from the tooth’s ECM, such as transforming growth factor (TGF)-β1, NGF, adrenomedullin, and hepatocyte growth factor, will act...
on stem/progenitor cells to stimulate recruitment/chemoattraction, proliferation, differentiation, and synthetic and secretory activity (mineralization events).

Subsequently, this organization of events will lead to dentin bridge formation at the lesion site and the restoration of the functional activity of the tooth. Notably, growth factors, such as TGF-β superfamily members, are well characterized in the signaling of tertiary dentinogenic events and have been shown to be present in the dentin ECM and released by bacterial acids and restorative materials that promote repair. Interestingly, the p38 MAP kinase signaling pathway, which has also been shown to be activated during inflammation, is also invoked by dentin ECM components and TGF-β signaling during repair processes. This convergent signaling highlights the potential interplay between inflammatory and regenerative events (58).

Figure 1. NF-κB nuclear translocation and proinflammatory gene expression is stimulated in dental pulp cells exposed to bacterial components and cytokines. (A) Preliminary (n = 1) nuclear:cytoplasmic ratio analysis of NF-κB (MAb NF-κB p65 subunit [clone F-6 diluted 1 : 100; Santa Cruz, Santa Cruz, CA]) at 1 hour in primary rodent dental pulp cells after stimulation as determined by high-content analysis (routinely performed by Imagen Biotech Ltd, Manchester, UK). (B) Example images at 1 hour of culture for (i) control (unstimulated) and (ii) proinflammatory stimulated (Escherichia coli LPS (10 μg/mL), Sigma-Aldrich, Gillingham, UK) pulp cells. NF-κB p65 staining is more diffuse and cytoplasmic in controls compared with the more intense nuclear localization in stimulated cells indicating increased nuclear translocation. (C) Representative gel images of relative gene expression levels at 4 hours of pulp cell exposure as assayed by reverse transcription polymerase chain reaction analysis for key (i) Toll-like receptors, (ii) NF-κB signaling components, and (iii) proinflammatory cytokines normalized to GAPDH housekeeping levels. Primers were designed from rodent sequences in GenBank. Stimulants for all experiments included E. coli LPS (10 μg/mL), S. mutans (heat-killed 100 bacteria per pulp cell), and TNF-α and IL-1β (both at 10 ng/mL, InvivoGen, San Diego, CA and Autogen Bioclear, Calne, UK, respectively). Controls were unexposed cells from the same time point. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MCP-1, monocyte chemoattractant protein 1; GMCSF, granulocyte macrophage colony-stimulating factor.
Interactions between Dental Tissue Inflammation and Regeneration

Because of the differences in the complexity of the 2 processes, the impact of the inflammatory response is likely to be different in reactionary compared with reparative dentinogenesis. Indeed, it would seem somewhat futile for tissue repair processes to be invoked if significant infection and inflammation are ensuing because of the tissue damage caused by both processes. Several lines of evidence now support the notion that only when the infection and inflammation are under control will repair events occur. Studies have directly shown that dental tissue repair is more successful in germ-free animals compared with animals with infected dental lesions (59–62). In addition, high levels of cytokines and growth factors, such as TNF-α and TGF-β, and dentin matrix components present during disease result in pulp cell death and impede stem cell differentiation processes (63–66). Conversely, when the infection is at a relatively early stage or has abated, cytokines will be at relatively low levels. Subsequently, proinflammatory molecules, such as TNF-α and ROS, at these concentrations can up-regulate p38 MAP kinase signaling, stem/progenitor cell differentiation and mineralization processes, and dentin sialoprotein and dentin phosphoprotein expression. Others have recently also shown the positive effect that the immune system can have on repair events by demonstrating how cytokine secretion by immunocompetent cells, such as macrophages and dendritic cells, can stimulate odontoblast differentiation (30, 67–70). Further indication of the cross talk between the 2 processes is also provided by data that show that molecules such as C5a and stromal cell–derived factor 1/ CXCL12, which are both up-regulated during various disease, can signal the recruitment of both immune and stem cells via their interaction with the C5AR/CD88 and C-X-C chemokine receptor 4, respectively. Notably, it is known that cytokines modulate C-X-C chemokine receptor 4 expression on stem cells, and this process may limit stem cell recruitment and activation during chronic disease (71–73).

Further indirect evidence of the link between inflammation and regeneration is potentially derived from the mode of action of restorative materials that promote regenerative events in vitro. Both calcium hydroxide and MTA are known to stimulate tertiary dentin bridge formation, and preceding the healing process, dental tissue inflammation is routinely histologically observed. It is proposed that hydroxyl ions derived from these setting restoratives raise local pH at the lesion site, resulting in chemical tissue irritation and cellular necrosis. It is known that necrotic cells release low levels of cytokines and other damage signals to facilitate the removal of the dead or dying cells, leading to a "sterile" inflammatory response. The levels of these molecules during this acute and resolving inflammatory phase may subsequently activate healing events within the pulp. In addition, calcium hydroxide and MTA have demonstrable antibacterial action, which may also facilitate infection resolution, and their release of bioactive components from dentin ECM may promote tissue repair (74–84).

Emerging Areas for Future Dental Therapy

Molecular approaches, including high-throughput transcriptional profiling of carious pulpal tissue, have recently indicated that proinflammatory processes rather than repair-associated molecular events predominate in diseased teeth (222). Further mining of these data subsequently identified a molecule novel to pulp biology called adrenomedullin, which was up-regulated during dental disease. This molecule is characterized as a pleiotropic growth factor/ cytokine that also has anti-bacterial and immunomodulatory properties and can stimulate mineralized tissue differentiation, secretion, and angiogenic events. Subsequent studies have now shown that ADM is sequestered within the dentin ECM and likely plays a role in dental tissue development (53). A more thorough characterization of similar large data sets has the potential to identify other novel molecular targets that may have therapeutic application.

Antioxidants may represent a class of molecules that may have utility in regulating dental tissue inflammation while enabling regenerative events. Interestingly, dental resins supplemented with the antioxidant N-acetyl-cysteine may modulate the activation of the key NF-κB pathway and subsequently limit the cycle of chronic inflammation (85). The protection of cells and tissues from ROS may also contribute to a more conducive environment for tissue repair and may indicate that a better understanding and characterization of the activity of other antioxidant molecules may identify novel dental treatment modalities.

Epigenetic regulating molecules, such as histone deacetylase inhibitors, also show promise for therapeutic application. A recent review highlighted the current knowledge of their mode of action, which involves DNA modification, and their therapeutic usefulness in nondental areas. In particular, it emphasized their anti-inflammatory properties and ability to promote differentiation and mineralization events necessary for bone engineering. Proof-of-principle studies have shown the ability of histone deacetylase inhibitors to promote both primary pulp cell differentiation and mineralization-related events (86–88). Therefore, further work is clearly needed to explore their anti-inflammatory activity in the context of the dentin-pulp complex and, subsequently, to determine whether these molecules could be used as an adjunctive therapy for dental tissue restoration.

Currently, several cellular approaches for the treatment of oral and dental diseases are emerging that relate to inflammation modulation. Notably, recent research has identified the ability of mesenchymal stem cells (MSCs) to modulate inflammatory processes. This immunomodulatory ability has been shown to occur as a result of cell-cell contact between MSCs and immune system cells, which results in the secretion of TGF-β and indolamine-2,3-dioxygenase-1, which can dampen the inflammatory response. Further studies have subsequently shown that via these interactions MSCs can inhibit proliferation, cytokine/antibody secretion, immune cell maturation, and antigen presentation in T cells, B cells, natural killer cells, and dendritic cells. In addition, because MSCs are immune privileged, potentially because of low-level major histocompatibility complex class II surface expression and their delivery to the dental tissue may have utility in not only dampening inflammation but also providing a cellular resource for tissue repair (89–93).

Recent studies using low-level light therapy (LLLT) have shown its potential application in dental tissue repair. Indeed, it has been shown that LLLT application in vitro can promote dental cell proliferation, energy metabolism, mitochondrial function, and mineralization events (94). The mechanism by which LLLT is proposed to work is via its action on mitochondrial cytochrome C oxidase. The absorbance of light by this molecule potentially leads to its dissociation from nitric oxide, which then allows cytochrome C oxidase to rebind oxygen and re-enter respiratory chain activity leading to adenosine triphosphatase synthesis and increased cellular activity. Notably, nitric oxide levels increase during inflammation and hence may “clog” mitochondrial function and metabolism. Work from other fields has now shown that the application of LLLT may be beneficial in the treatment of inflammatory diseases (95). Combined, these data now suggest that the application of LLLT at the appropriate wavelength and power could be used to modulate dental pulp inflammation while promoting repair events.

Conclusions

A recent review (96) on bone regeneration provided similar conclusions to those proposed here in that chronic and relatively high levels
of inflammation may inhibit the body’s attempts at repair, whereas relatively low-level inflammation may be beneficial in stimulating bone metabolic activity and regeneration. In addition, it is interesting to speculate that age-related changes along with associated immunosenescence may also regulate differentiation and mineralization events that occur in older individuals in the dentin-pulp complex. Indeed, senescent fibroblasts release proinflammatory molecules (51); it is therefore interesting to speculate that as the dental pulp tissue ages, such cells may provide nucleation foci for pulp stone formation because of their low-level cytokine release. It is conceivable that from an energetics standpoint the body may feel it futile to invest molecular and cellular energy into repair when tissue is under constant attack from invading bacteria and its own cells. However, if the infection is controlled, up-regulation of repair activity within the tooth would likely be of benefit and can subsequently “wall off” compartmentalize the invading bacteria. Therefore, further research into the interaction between the inflammatory and regenerative responses within the dentin-pulp complex is warranted.

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Pulp Regeneration—Translational Opportunities

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