

Review**The Role of Inflammatory Cytokines in Dental Caries Repair**Mahsa Farshbaf Antik^{1*}

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Abstract:

Dental caries is being considered as the most common noncommunicable disease worldwide. It is being defined as sugar-driven, biofilm mediated and dynamic disorder which causes remineralization and demineralization of teeth hard tissues involving inflammatory system. It has been shown that IL-6, IL-8 and TNF- α was significantly increased in saliva of patients with dental caries. A cascade of four steps is required to repair dental pulp by direct capping with calcium hydroxide or by implanting bioactive extracellular matrix molecules: moderate inflammation, commitment of adult reserve stem cells, proliferation, and differentiation of these cells. Osteoblast/odontoblast-like differentiation and expression of mineralization-related ECM molecules may also be promoted by mild inflammation of antigen-presenting dendritic cells. Studies in humans and in vitro indicate that dentin barrier formation occurs only when pulp inflammation and infection are minimized, allowing for tissue homeostasis to return. To ensure the sustainability of dental treatments, promoting the resolution of pulp inflammation may be a valuable therapeutic opportunity. The potential significance of the initial inflammatory reaction is highlighted by experimental data obtained on pulp repair of healthy and carious teeth. In experimental capping of exposed sound pulps or after implantation of bioactive molecules at ectopic sites, this initial step appears to be linked to the activation of dormant or latent progenitors. We have reviewed the role inflammation in caries repair in this study.

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Introduction

Dental caries is being defined as dynamic disease resulting in demineralization and remineralization of tooth which is often due to imbalance between protective and pathological mechanisms (1). Although the oral hygiene has improved over the last decades, the prevalence of dental caries remains high. First molar occlusal surfaces and buccal surfaces of lower first molars with pits are most susceptible to carious lesions (2). Dental caries caused more than 4000 Disability Adjusted Life Years (DALY) with over 2 billion cases globally (3). Dental caries is dynamic condition involving microorganisms, oral environment and host factors (2). We have reviewed the role of inflammation in dental caries repair in this study.

Dental caries and inflammation

Gram-positive saprophytic bacteria on erupted human teeth are harmful. Biofilms attach to thick enamel and protect the underlying dentin and dental pulp from microorganisms and bacteria. However, these bacteria produce acids that gradually demineralize enamel when they are placed in a sugar-rich environment (4). Gram-positive bacteria, such as streptococci, lactobacilli, and actinomyces, are primary degraders of dentin when the enamel barrier is compromised (5). An antibacterial, immune, and inflammatory response is triggered when host cells recognize bacterial components at the dentin-pulp interface. When associated with the formation of dentin at the pulp-dentin interface, these events could eliminate early-stage bacterial infection. Almost always, chronic pulp inflammation results from unchecked bacterial invasion after a long period of chronic inflammation. In the following days, pulp necrosis, infection of the root canal system, and periapical disease may develop (5, 6). Since they are located at the pulp-dentin interface and their long cellular processes embed in dentin tubules,

odontoblasts are the first pulpal cells in contact with dentin-invading pathogens and their products.

PAMPs are Pathogen-Associated Molecular Patterns (PAMPs) that are sensed by Pattern-Recognition Receptors (PRRs). Toll-like receptors (TLR) are one class of PRRs that play an essential role in triggering the innate immune response's effector phase (7). There is evidence that TLR2 and TLR4, respectively, are involved in the detection and sensing of Gram-positive and Gram-negative bacteria in healthy pulp odontoblasts. These pathogens are recognized by odontoblasts when they diffuse through dentin tubules during carious infection (8, 9). Innate immunity effectors are upregulated by TLR activation, such as antimicrobial agents and proinflammatory cytokines and chemokines, increasing the recruitment and activation of inflammatory cells both in the tissue and across the blood vessels (10). There are many aspects of the local immune response that are regulated by IL-6, a synthetic cytokine produced by immune and nonimmune cells (11). As a result of TLR2 stimulation, its expression is strongly increased in bacteria-challenged inflamed pulps *in vivo* and in odontoblasts *in vitro* (12, 13). IL-6 is critical in order to activate differentiation and regulation of T helper (Th)2, Th17, and T regulatory (Treg) cells, and also increasing the secretion of acute-phase proteins including lipopolysaccharide-binding proteins (14). IL-8 is constitutively expressed by odontoblasts, likely in anticipation of disease, and its levels can be upregulated by bacterial components. (e.g., LPS sends signals through TLR) IL-1 and TNF- in various cell types (15). Neutrophils, which are typically one of the first immune cell types to be present at the site of infectious disease, are particularly important for neutrophil recruitment and activation, which depends on IL-8.

Dental repair and immune system

As previous studies discussed the role of odontoblasts and pulp fibroblasts regulating the dental pulp immune and inflammatory responses to caries and suggested that interactions between immune cells and odontoblasts influence the pulp repair process (16-18). As we have previously mentioned when dental pulp is being invaded by bacteria dendritic cells (DC) migrate to the area near antigens (19). Other immune cells including T-cells, B-cells and macrophages invade the area and starting the inflammation process. The fast accumulation of DCs into the odontoblast layer at some point of the early segment of pulp restore has recommended that odontoblast-derived chemotactic molecules might be responsible for the recruitment of DCs that ensure immunosurveillance of pulp tissue (20). Other *in vitro* studies also suggested the role of odontoblasts in triggering the inflammatory response to invading bacteria (8, 17).

DCs and odontoblasts are close to each other in the peripheral pulp under caries lesions. This suggests that DCs may play a role in odontoblast differentiation and/or in regulating their synthesis activity (21). It is still unknown whether or not DCs in inflammatory dental pulp tissue produce these factors *in vivo*. CCL20, a chemokine produced by activated DCs and other cells, may have a direct effect on odontoblasts and/or their precursors (22, 23). Clinically, pulp repair occurs following calcium hydroxide capping when bacterial contamination and inflammation are minimal. When there is a long-lasting, chronic infection, which always leads to pulp necrosis, the tooth cannot be fixed (24). Cytokines are low when the infection is early or has subsided. Proinflammatory molecules, such as TNF- α and Reactive Oxygen Species (ROS), can then up-regulate p38 MAP kinase signaling, stem/progenitor cell differentiation and mineralization processes, and dentin sialoprotein and dentin phosphoprotein

expression at these concentrations. Others have recently demonstrated how cytokine secretion by immunocompetent cells such as macrophages and dendritic cells can stimulate odontoblast differentiation, demonstrating the positive effect that the immune system can have on repair events (25-27).

There may be more indirect evidence of the link between inflammation and regeneration in the way that materials that promote regeneration in living organism. Calcium hydroxide and MTA are known to stimulate the formation of tertiary dentin bridges, and dental tissue inflammation is routinely observed histologically prior to the healing process. The levels of these molecules during this acute and resolving inflammatory phase may subsequently activate healing events within the pulp (28, 29).

Conclusion

In conclusion, the potential significance of the initial inflammatory reaction is highlighted by experimental data obtained on pulp repair of healthy and carious teeth. In experimental capping of exposed sound pulps or after implantation of bioactive molecules at ectopic sites, this initial step appears to be linked to the activation of dormant or latent progenitors. Over the course of many years, the significance of inflammation in the process of pulp healing has been grossly underestimated. Inflammation has been viewed as nothing more than an unfavorable effect that, in most cases, results in pulp necrosis. In light of recent findings, the inflammatory process ought to be reexamined in order to gain a better comprehension of the potential benefits that could result from this process.

References

- 1.Pitts NB, Zero DT, Marsh PD, Ekstrand K, Weintraub JA, Ramos-Gomez F, et al. Dental caries. *Nature Reviews Disease Primers*. 2017;3(1):17030.

2. Schwendicke F, Frencken J, Innes N. Caries excavation: evolution of treating cavitated carious lesions: Karger Medical and Scientific Publishers; 2018.

3. Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, et al. Global burden of oral conditions in 1990-2010: a systematic analysis. *J Dent Res.* 2013;92(7):592-7.

4. Farges JC, Keller JF, Carrouel F, Durand SH, Romeas A, Bleicher F, et al. Odontoblasts in the dental pulp immune response. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution.* 2009;312(5):425-36.

5. Love R, Jenkinson H. Invasion of dentinal tubules by oral bacteria. *Critical reviews in oral biology & medicine.* 2002;13(2):171-83.

6. Heyeraas K, Berggreen E. Interstitial fluid pressure in normal and inflamed pulp. *Critical Reviews in Oral Biology & Medicine.* 1999;10(3):328-36.

7. Beutler B. Microbe sensing, positive feedback loops, and the pathogenesis of inflammatory diseases. *Immunological reviews.* 2009;227(1):248-63.

8. Veerayutthwilai O, Byers M, Pham TT, Darveau R, Dale B. Differential regulation of immune responses by odontoblasts. *Oral microbiology and immunology.* 2007;22(1):5-13.

9. Jiang H-W, Zhang W, Ren B-P, Zeng J-F, Ling J-Q. Expression of toll like receptor 4 in normal human odontoblasts and dental pulp tissue. *Journal of endodontics.* 2006;32(8):747-51.

10. Viola A, Luster AD. Chemokines and their receptors: drug targets in immunity and inflammation. *Annu Rev Pharmacol Toxicol.* 2008;48:171-97.

11. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nature immunology.* 2015;16(5):448-57.

12. Farges J-C, Carrouel F, Keller J-F, Baudouin C, Msika P, Bleicher F, et al. Cytokine production by human odontoblast-like cells upon Toll-like receptor-2 engagement. *Immunobiology.* 2011;216(4):513-7.

13. Nibali L, Fedele S, D'aiuto F, Donos N. Interleukin-6 in oral diseases: a review. *Oral diseases.* 2012;18(3):236-43.

14. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research.* 2014;1843(11):2563-82.

15. Levin LG, Rudd A, Bletsas A, Reisner H. Expression of IL-8 by cells of the odontoblast layer in vitro. *European Journal of Oral Sciences.* 1999;107(2):131-7.

16. Goldberg M, Smith AJ. Cells and extracellular matrices of dentin and pulp: a biological basis for repair and tissue engineering. *Critical Reviews in Oral Biology & Medicine.* 2004;15(1):13-27.

17. Staquet M-J, Durand S, Colomb E, Romeas A, Vincent C, Bleicher F, et al. Different roles of odontoblasts and fibroblasts in immunity. *Journal of dental research.* 2008;87(3):256-61.

18. Jontell M, Okiji T, Dahlgren U, Bergenholz G. Immune defense mechanisms of the dental pulp. *Critical Reviews in Oral Biology & Medicine.* 1998;9(2):179-200.

19. Jontell M, Bergenholz G, Scheynius A, Ambrose W. Dendritic cells and macrophages expressing class II antigens in the normal rat incisor pulp. *Journal of dental research.* 1988;67(10):1263-6.

20. Farges J-C, Romeas A, Melin M, Pin J-J, Lebecque S, Lucchini M, et al. TGF- β 1 induces accumulation of dendritic cells in the odontoblast layer. *Journal of dental research.* 2003;82(8):652-6.

21.Ohshima H, Sato O, Kawahara I, Maeda T, Takano Y. Responses of immunocompetent cells to cavity preparation in rat molars: an immunohistochemical study using OX6-monoclonal antibody. *Connective tissue research*. 1995;32(1-4):303-11.

22.Marcet B, Horckmans M, Libert F, Hassid S, Boeynaems JM, Communi D. Extracellular nucleotides regulate CCL20 release from human primary airway epithelial cells, monocytes and monocyte-derived dendritic cells. *Journal of cellular physiology*. 2007;211(3):716-27.

23.Nakanishi T, Takahashi K, Hosokawa Y, Adachi T, Nakae H, Matsuo T. Expression of macrophage inflammatory protein 3 α in human inflamed dental pulp tissue. *Journal of Endodontics*. 2005;31(2):84-7.

24.Goldberg M, Farges J-C, Lacerda-Pinheiro S, Six N, Jegat N, Decup F, et al. Inflammatory and immunological aspects of dental pulp repair. *Pharmacological Research*. 2008;58(2):137-47.

25.Goldberg M, Farges J-C, Lacerda-Pinheiro S, Six N, Jegat N, Decup F, et al. Inflammatory and immunological aspects of dental pulp repair. *Pharmacological research*. 2008;58(2):137-47.

26.Paula-Silva F, Ghosh A, Silva L, Kapila Y. TNF- α promotes an odontoblastic phenotype in dental pulp cells. *Journal of Dental Research*. 2009;88(4):339-44.

27.Saito K, Nakatomi M, Ida-Yonemochi H, Kenmotsu S-i, Ohshima H. The expression of GM-CSF and osteopontin in immunocompetent cells precedes the odontoblast differentiation following allogenic tooth transplantation in mice. *Journal of Histochemistry & Cytochemistry*. 2011;59(5):518-29.

28.Schröder U. Effects of calcium hydroxide-containing pulp-capping agents on pulp cell migration, proliferation, and differentiation. *Journal of dental research*. 1985;64(4):541-8.

29.Kardos T, Hunter A, Hanlin S, Kirk E. Odontoblast differentiation: a response to environmental calcium? *Dental Traumatology*. 1998;14(3):105-11.