MOLECULAR MECHANISMS OF DENTINE-PULP COMPLEX RESPONSE INDUCED BY MICROBIOME OF DEEP CARIES

Iliescu Alexandru-Andrei¹, Paula Perlea², Gheorghiu Irina-Maria³, Mitran Mihai⁴, Mitran Loredana⁵, Moraru Iren⁶, Scărlătescu Sînziana⁷, Şachir Erdoğan⁸, Iliescu Andrei⁹

1 Department of Oral Rehabilitation, Faculty of Dental Medicine, UMF Craiova

2 Department of Endodontics, Faculty of Dental Medicine, UMF "Carol Davila" Bucharest

3 Department of Restorative Odontotherapy, Faculty of Dental Medicine, UMF "Carol Davila" Bucharest

4 Department of Obstetrics and Gynecology, Faculty of Medicine, UMF "Carol Davila" Bucharest

5 Department of Otorhinolaryngology, Elias Hospital

6 Department of Odontology, Faculty of Dental Medicine, UMF Craiova

7 Department of Endodontics, Faculty of Dental Medicine, UMF "Carol Davila" Bucharest

8 Department of Endodontics, Faculty of Dental Medicine, University Ovidius Constanța

9 Department of Endodontics, Faculty of Dental Medicine, UMF "Carol Davila" Bucharest

Irina Maria Gheorghiu

Faculty of Dental Medicine, UMF "Carol Davila" Bucharest

Calea Plevnei 17-23, Bucharest

email: igheorghiu@hotmail.com

ABSTRACT

Deep caries progress is associated with tertiary dentin formation and additional reversible or irreversible dental pulp inflammation. It seems that some particular signs of pain in irreversible pulpitis are associated to a particular caries microflora. Streptococcus species, Parvimonas micra and Dialister invisus are prevailing in cases of throbbing pain while Streptococcus mutans is incriminated in sensitivity to vertical percussion of tooth. Continuous pain is thought to be the clinical outcome of Lactobacillus implication. A better understanding of molecular signals and mechanisms induced by microbiome of deep caries that orchestrate the modulation of dental pulp complex response toward tertiary dentinogenesis or pulp inflammation it is supposed to improve diagnosis and conservative therapies of vital pulp.

Keywords: deep caries; microbiome; tertiary dentine; molecular signals.

Introduction

Tertiary dentin is formed as a protective response of the dental pulp to external irritations, mainly caused by attrition or caries progress, and cavities preparation/filling finally resulting in the thickening of mineralized barrier that separates the pulp chamber from oral microbial milieu (1).

Commonly the tertiary dentin emerging as secretion product of primary (native) odontoblasts is termed reactionary dentin unlike the reparative dentin, which is produced by newly differentiated secondary odontoblasts, the so called odontoblast-like cells (2). The reactionary dentin mirrors a slowly progressing external

aggression that allows the survival of primary odontoblasts. Regarding the reparative dentin, its secretion relies on a much more complex mechanism. Due to the intensity of irritant, the primary odontoblasts die and they are replaced by new cells, the odontoblast-like cells, which mimic the early formative stage of dentin-pulp complex despite their different profile of gene expression as compared to native odontoblasts (3,4). Sometimes in rapidly progressing deep caries an additional type of dentin, fibrodentin, may be temporary laid down until its reversal in reparative dentin (5).

As known all pulp injuries occurred during caries activity and its subsequent conservative

treatment aiming to preserve the vitality are producing local histological modifications in dentin-pulp complex including the tertiary dentin development. In recent years the advances in biomarkers and stem cells field opened a new window to understanding the molecular mechanisms that regulate the tertiary dentin secretion and mineralization (6).

In this paper are reviewed the main molecular signals and mechanisms induced by microbiome of deep caries that orchestrate the modulation of dental pulp complex response while generating the tertiary dentin and/or additional reversible pulp inflammation.

Deep caries microbiome

Traditional endodontology holds the concept of sterile pulp cavity in caries free and periodontal stable teeth. However, shifting from previous culturing methods to modern microbial molecular technologies such PCR combined with HT (high-throughput) DNA sequencing, it was revealed the existence at least transiently of microorganisms even inside the pulp of presumed clinically healthy teeth (7,8). Such microorganisms, having commensal or beneficial interrelations with host, are termed microbial symbionts (7,9).

A recent study identified in clinically healthy pulp tissue of pristine teeth a dominant community of bacteria (43% - 78%) belonging to *Ralstonia*, *Acinetobacter* and *Staphylococcus* genera. Additional to this core group there were also found to a lesser extent bacteria from genus *Micrococcus*, *Corynebacterium*, *Burkholderia* or family *Enterobacteriaceae*, and *Micrococcaceae*. This microbiome achieved the endodontic healthy system by transient bacteremia without to follow an external ingress pathway, such as caries or exposed dentinal tubules (7).

Once again it was proved that also blood-borne bacteria potentially may settle transitory in vital pulp regardless of its healthy or inflammatory status. The genus *Ralstonia* is involved in nosocomial infections as well as the genus *Acinetobacter*, an opportunistic pathogen. Though commensal the gram-positive facultative anaerobic genus *Staphylococcus* may also become an opportunistic pathogen. Jointly

Ralstonia, *Acinetobacter* and *Staphylococcus* genera contributed to less than 10% of total blood-borne microbiome (7).

The main pathogens involved in dental caries are oral species of *Streptococcus*, *Lactobacillus*, *Neisseria*, *Actinomyces*, and *Veillonella* (10). Some of them might be also implicated in the onset of pulp inflammation and its transition to irreversible acute or chronic pulpitis (11,12). However, commonly the microflora of deep caries is completely different compared to dominant microorganisms genera found in infected root canals, such as *Porphyromonas*, *Prevotella*, *Peptostreptococcus*, *Fusobacterium*, and others (13,14).

The microbiome of deep caries and reversible pulpitis is almost similar in occlusal vs. proximal lesions, and in posterior vs. anterior teeth. In the highest proportion were found Firmicutes (*Streptococcus*, *Lactobacillus*, *Pseudoramibacter*) and Actinobacteria (*Actinomyces*, *Propionibacterium*, *Olsenella*). Moreover, there are increasing proves supporting the putative connection in deep caries and reversible pulpitis between pain evoked by cold or heat and the activity of *Actinomyces* and *Veillonellaceae* unidentified species (12).

A recent reappraisal of microbiome in initial caries found out that between acidogenic and aciduric bacteria, namely *Streptococcus* and *Lactobacillus* is installed a synergistic relationship. Since *Lactobacillus* is the most resistant aciduric microorganism at low pH, the diversity of microflora in deep caries is progressively reduced and this bacterium gets the position of dominant genus (12).

Unlike the reversible pulpitis associated to deep caries, where microbiome practically remains unchanged this conversion of microbial composition characterized by Firmicutes supremacy result in occurrence of a symptomatic irreversible pulp inflammation (12).

Actually in very deep caries there is a coexistence of pathogens. Some of them, such as *Streptococcus mutans*, *Atopobium genomospecies C1*, and *Veillonella species* are prevalent in advanced caries, while *Parvimonas micra*, *Pseudoramibacter alactolyticus*, and *Fusobacterium nucleatum* are especially harbored in infected root canals. It has to be mentioned

that *Parvimonas micra* and *Pseudoramibacter alactolyticus* are also present in deep caries correlated with pulp exposure (15).

In painful irreversible pulpitis it seems that *Streptococcus* species, *Parvimonas micra* and *Dialister invisus* are associated with throbbing pain while *Streptococcus mutans* is responsible for sensitivity to vertical percussion of tooth. Relating to the clinical symptom of continuous pain *Lactobacillus* might be in prevailing position (Figure 1). However, sometimes in painful pulp inflammations are also implicated various anaerobic bacteria capable to release lipopolysaccharides, ammonia and indole (15).

Microbiome metabolic by-products in deep caries

The main pathway of bacterial metabolic by-products released in deep caries to directly approach the pulp tissue are the dentinal tubules opened by caries progress. In active caries predominant among the metabolic by-products are organic acids such as lactic, propionic, and acetic acid (16).

Along with aforementioned organic acids, mainly implicated in demineralizing the dentine, a specific by-product released extracellularly at low pH by acidogenic Gram-positive bacteria is lipoteichoic acid, which alike to lipopolysaccharides released by anaerobic Gram-negative also found in deep caries, activate the innate immune system following same molecular pathways (16,17).

The clinical outcome of long period irritation produced due to the metabolic by-products of bacteria that colonize the deep caries result in painful pulpal syndrome. Paradoxically, compared to other living tissues, the lactic, acetic or propionic acid do not evoke pain in contact cu A-δ nerves located in dentinal tubules, and even suppress the intratubular nerve excitation through other irritants (16).

Relying on real-time polymerase chain reaction the deep caries lesions are microbiologically categorized in 4 classes: high-Lactobacillus, high-Prevotella, mid Lactobacillus/Prevotella, and low Lactobacillus/Prevotella (18). In high-Lactobacillus lesions does not occur sensibility to cold or heat but in

high-Prevotella ones is present a tooth sensibility to heat, possible facilitated due to the increased amounts of metabolic by-products like indole and ammonia. The high prevalence of streptococci in advanced caries is thought to be responsible of double tooth sensibility to thermal irritants cold and heat. However, in this case the pain mechanism is triggered by pro-inflammatory cytokines. Prevotella is also using the similar pathway of inflammation mediators in eliciting pain at cold and heat stimuli (16).

Figure 1 – Microorganisms involved in releasing painful stimuli.

Moreover, the metabolic activity of anaerobic Gram-negative bacteria in deep caries might be also considered an explanation of pulpal pain as, by activating Hageman factor, they are indirectly contributing to bradykinin release (19).

The bacterial metabolic by-products such as organic acids, ammonia, and indole are collectively incriminated in evoking the continuous pain that clinically characterize the acute irreversible pulpitis (16).

Dentine-pulp complex - a reservoir of growth factors and bioactive molecules

During the dental caries progress toward the pulp the well known defensive response of dentine-pulp complex lies in making up of tertiary dentine. When the carious attack is mild the native odontoblasts survive and trigger a reactionary dentinogenesis. Nevertheless, if the cariogenic bacteria are more aggressive the native odontoblasts die and the dentine-pulp complex

response relies on reparative dentinogenesis, which is secreted by odontoblast-like cells (20).

In both cases throughout the secretion and mineralization of newly formed predentine a lot of bioactive molecules like growth factors and cytokines residing in extracellular matrix are activated and afterward progressively entrapped and sequestered in tertiary dentine (20,21).

This complex cocktail of bioactive molecules, commonly based on noncollagenous proteins is characterized by components such as growth factors (Figure 2), neurotrophic factors (Figure 3), extracellular matrix molecules (Figure 4), cytokines, neuropeptides, and others (6).

In tertiary dentinogenesis are implicated more classes of bioactive molecules acting either individually or synergistic. The best investigated growth factors aiming to induce this process are transforming growth factor β -1 (TGF- β 1), bone morphogenetic protein-2 (BMP-2), bone morphogenetic protein-4 (BMP-4), bone morphogenetic protein-7 (BMP-7), fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-2 (IGF-2). However, it seems that even the activity of main growth factors as TGF- β 1, BMP-2 and FGF-2 at their turn is regulated directly or indirectly by extracellular matrix protein PLAP-1 that is released in periodontal ligament (Figure 2)(6,20).

Obviously, before the initiation of tertiary dentine secretion it has to be obtained the cellular basis of dentinogenesis, which means the replacement of destroyed primary odontoblasts during caries advancement with novel secretory cells, the odontoblast-like cells. Accordingly, the proliferation and differentiation of stem cells from dental pulp (DPSC), or apical papilla (SCAP) into odontoblast-like cells are crucial. Among the growth factors having in charge this objective are BMP-2, BMP-4, BMP-7, adrenomedullin (ADM), TGF- β 3, and platelet-derived growth factor (PDGF) (6,20,21,22).

Figure 2 – Growth factors as signaling molecules.

Figure 3 – Contributing neurotrophic factors in tertiary dentine formation.

Figure 4 – Extracellular matrix molecules of tertiary dentine.

In the odontoblast-like cells differentiation and tertiary dentine secretion are also involved neurotrophic factors like glial cell line-derived growth factor (GDNF) and nerve growth factor (NGF) (Figure 3), as well as some others bioactive molecules represented by Semaphorin 3A (Sema3A) and Copine 7 (CPN7). Sema3A

is also involved in chemotaxis, migration, and differentiation of DPSC (6,20, 23-25).

Contributory to later mineralization of initially secreted tertiary dentine are TGF- β 2, IGF-1, and IGF-2 that induce from DPSC and SCAP newly differentiated odontoblast-like cells showing mineralizing phenotypes (Figure 2) (6,20,21).

However, the pivotal role in mineralization of tertiary dentine has to be rendered to a lot of extracellular matrix noncollagenous proteins, as follows: dentine matrix protein-1 (DMP-1), dentine sialophosphoprotein (DSPP), dentine phosphoprotein (DPP), and small leucine-rich proteoglycans (SLRPs). Particularly involved in hydroxyapatite crystal formation are DPP and bone sialoprotein (BSP). However, some bioactive molecules of extracellular matrix like osteopontin (OPN) or matrix extracellular phosphoglycoprotein (MEPE) demonstrated an inhibitory effect in hydroxyapatite crystal formation and mineralization process (Figure 4) (6,20,26).

Cascades of molecular events induced by deep caries progress

The dentine-pulp response to microbiome aggression during the deep caries advancement is actually an instable balance between tertiary dentine feedback and inflammatory pulp reply, the latest one also oscillating between acute and chronic processes (Figure 5).

Figure 5 – Cascades of molecular events in tertiary dentinogenesis.

To effectively play their role in healing of damaged pulp by forming reactionary or reparative tertiary dentine, the signaling molecules interact within a particular pathway of molecular events. Accordingly, these molecules have to be implicated in cell proliferation (FGF-2), differentiation (TGF- β 1), chemotaxis and cell homing (IL-8, TGF- β 1), or angiogenesis (VEGF) (6,27).

First step in inducing the secretory activity of odontoblasts or odontoblasts-like cells is to prompt the signaling transduction pathway of mitogen activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin pathway (PI3K/AKT/mTOR), which regulates many cellular events such as proliferation, migration, adhesion, and apoptosis (6, 28).

In fact the MAPK pathway symbolizes a big family regulating the molecular events cascades made up from 3 subfamilies: p38 mitogen-activated protein kinase (p38 MAPK) pathway, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, and c-jun N-terminal kinase (JNK) pathway (6).

In addition to its central role of transcriptional control in order to initiate and maintain the secretory activity of odontoblasts, p38 MAPK is also in charge of odontoblasts-like cells delivery, starting with the stem cells proliferation and their later differentiation in specialized cells (22,29,30).

In deep caries c-jun N-terminal kinase (JNK) pathway joins to the response of molecular cascades subsequent to environmental stress (bacterial organic acids, cold and heat stimuli) and initial involvement of growth factors or further connection of proinflammatory cytokines (6).

Transforming growth factor β /small mother against decapentaplegic (TGF β -Smad Signaling) pathway is activated by bioactive molecules TGF- β 1 and BMP-2, which act specifically: TGF- β 1 on SMAD 2,3,4 proteins respectively BMP-2 on SMAD 1,5,8 proteins (31).

Excepting MAPK super family, another basic pathway involved in tertiary dentinogenesis is the Wnt/ β -catenin signaling pathway (also termed canonic pathway), which supports odontoblasts differentiation and proliferation. The

molecular cascade regulated by Wnt/ β -catenin signaling pathway increases the cytoplasmic accumulation of β -catenin and afterwards its translocation in the cell nucleus, activating the transcriptional factor Runx2, a putative promoter of odontoblasts differentiation (23,32,33).

Though unwanted, in deep caries advancement usually can not be avoided an inflammatory pulpal response, which requires the approach of Key Nuclear Factor kappa β (NF- κ β) pathway as well as p38 MAPK, ERK, and JNK pathways (6, 34).

NF- κ β may be considered a prevailing signaling pathway involved in development of pulp inflammation. Due to its initiation, translocation in cell nucleus and initiation of target genes expression, in deep caries NF- κ β is also strongly involved in stress responses of dental pulp to carious stimuli and orchestrates both innate and adaptive immune feed back (6, 35).

A reduced activity of NF- κ β and p38 MAPK signaling cascades, therapeutic induced, might result in avoiding the pulp tissue damage by down regulating proinflammatory cytokines and chemokines that monitor the immune cells recruitment. Moreover, the dentine-pulp complex repair may also occur when proinflammatory mediators are maintained at low level (36).

Understanding the cascades of molecular events coordinated by dentine-pulp complex as defensive reparatory response to deep caries progress, might be expected improved diagnostic and therapeutic conservative procedures in future daily endodontic practice.

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