

Review

Cariogenic microorganisms of dental plaque or acid produced by bacteria may induce an increase of acid produce of Non-mutans streptococci

¹Li M. Y., ²Lai G. Y. and ^{*3}Wang J.

¹Shanghai Key Laboratory of Stomatology, Shanghai Research Institute of Stomatology, Ninth People's Hospital, Medical College, Shanghai Jiao Tong University, 639 Zhizaoju Road, Shanghai 200011, P.R.China.

²Department of Restorative Dentistry and Periodontology, Dental School of the Ludwig-Maximilians-University, Goethestr. 70, D-80336, Munich, Germany.

Abstract

It is well known that dental caries is mainly caused by acids from bacterial fermentation. Acidogenic bacteria, such as Mutans streptococcus and Lactobacilli, have been considered as major pathogenic factors of dental caries for a long time. Whereas various studies have shown that Non-mutans streptococci can adhere to dental hard tissues, and can secrete GTF enzyme and produce organic acids, which may implicate the cariogenic capability of theirs to destroy dental tissue. With their capabilities, non-mutans streptococci may be proposed to play a role in dental caries process, especially at the initial stage. We proposed that cariogenic microorganisms (especially Mutans streptococcus and Lactobacilli) or acid production by bacteria may affect the virulence properties of non-mutans streptococci (especially *S. sanguinis*), inducing an increase of the acid produce. Paying attention to the role of non-mutans streptococci in the progression of dental caries may advance the knowledge of pathology and etiology of caries and offer alternatives for the prevention and therapy of dental caries.

Keywords: Non-mutans streptococci; dental caries; acidogenic; mutans streptococcus.

INTRODUCTION

Non-mutans streptococci, a member of streptococci species except *S. mutans*, including *Streptococcus sanguinis* (*Streptococcus sanguis*), *Streptococcus gordonii*, *Streptococcus oralis* and *Streptococcus mitis*, have been recognized as a key player in the bacterial colonization of the mouth long before (Kolenbrander et al., 2002). They are ones of the first colonization pioneers during the plaque formation and provide certain micro-ecological environment factors for plaque formation (Hojo et al., 2009); On the other hand, they may serve as tethers for the attachment of other oral microorganisms, which colonize the tooth surface, form dental plaque, and contribute to the development of caries and periodontal disease (Wang et al., 2010). Dental caries has been con-

sidered to be the consequence of demineralization of susceptible dental hard tissues caused by organic acids (Fejerskov and Kidd, 2008). For the hypothesis theory relating plaque to caries, there was a shift in opinion. Firstly, the Non-Specific Plaque Hypothesis was proposed, which regards dental caries as the result of the outcome of the interactions among all of the species. Then the Specific Plaque Hypothesis was presented, which considers a restricted subset of species to be responsible for this disease, such as *S. mutans* and *Lactobacillus*. Recently, the Ecological Plaque Hypothesis is put forward, which deems caries will develop only when the homeostatic balance of the resident microflora is broken due to a change in local environmental conditions (Loesche, 1979 and Marsh, 1994).

As for this new field, Kreth and Takahashi's research, which intends to understand the complex interactions of oral bacteria, represents the latest hotspot. It has been

*Corresponding Author E-mail: Imy1691@hotmail.com;
Tel (FAX): (021) 63135412

found that exogenous H₂O₂ causes release of DNA from *S. sanguinis* (Kreth et al., 2009) and catabolite control protein A controls hydrogen peroxide production and cell death in *S. sanguinis* (Zheng et al., 2010). The interspecies interactions are possibly mediated through bacteriocins and hydrogen peroxide. Bacteriocins produced by *S. mutans* are cytotoxic toward *S. gordonii* and *S. sanguinis*, whereas *S. gordonii* and *S. sanguinis* differentially produce H₂O₂ under aerobic growth conditions, which is relatively toxic toward *S. mutans* (Kreth et al., 2005 and Kreth et al., 2008).

As an extension of ecological plaque hypothesis, the importance of non-mutans streptococci was proposed by Takahashi. Takahashi and Nyvad go one step further and present a new view of caries. It is no longer just important to consider, which specific bacteria are present, but rather what those bacteria are doing. Under the acid environment, non-mutans streptococci may prompt the production of acid and induce demineralization (Ashby et al., 2009). *Actinomyces* spp. and non-*S. mutans* streptococci were detected at high levels in caries initiation, which may be involved in the initiation of the disease (Aas et al., 2008). These microbial acid-induced adaptation and selection processes may induce a shift of the demineralization/remineralization balance toward net mineral loss, leading to the initiation/progression of dental caries (Takahashi and Nyvad, 2010). The theory was supported by the observations that the low pH generated from sugar metabolism rather than sugar availability, and it led to the breakdown of microbial homeostasis in dental plaque (Marsh, 2006). The selection pressure for the acidogenic/aciduric bacteria in a mixed culture biofilm was account for the pH but not sugar availability. Accordingly, we wonder whether the residence of *S. mutans* and *Lactobacillus* could be speculated partly as a result of disease rather than the causes only or as a result in the lesions and thus more likely to form a vicious circle? But there are no more evidences yet.

Hypothesis

The acidogenic and aciduric bacteria in dental plaque, especially Mutans streptococcus and Lactobacilli, have been considered as major pathogenic factors of dental caries for a long time (O'Sullivan et al., 2000). But they may have not been regarded as very essential factors for initial carious lesions. Therefore, we hypothesize that non-mutans streptococci play a role in the initial phrase of dental caries due to their capabilities. Accordingly, cariogenic microorganisms (especially Mutans streptococcus and Lactobacilli) or acid produced by bacteria may affect the virulence properties of non-mutans streptococci. These would affect other plaque bacteria in the mouth also, resulting in an increase of the acid produce.

DISCUSSION

It can be concluded that some researchers have shown the support for this hypothesis. ① Horizontal gene transfer (HGT) is thought to play an important role in the evolution of species and innovation of genomes. The percentage of bacterial horizontally transferred genes varied from 30% to 50% (In-Geol and Sung-Hou, 2007). The gene transfer can occur from *T. denticola* to *S. gordonii* (Wang et al., 2002). These HGT may induce the transformation of bacterial virulence. ② Extended Ecological Plaque Hypothesis of Takahashi purports that in the presence of low pH, the non-MS bacteria can adapt themselves to the acid environment and produce acid. The acid will destabilize the homeostatic biofilm and shift it to a more overall acidogenic plaque biofilm (Takahashi and Nyvad, 2008). These microbial acid-induced adaptation and selection processes may lead a shift of the demineralization/remineralization balance toward to net mineral loss, leading to initiation/progression of dental caries (Takahashi and Nyvad, 2011). Moreover, when non-MS bacteria were exposed to an acidic environment, their acidogenicity may increase (Takahashi and Yamada, 1999). *S. mutans* would provide this acidic environment. Such situation may exist in white spot lesions at the beginning of caries. It would produce lower pH, thereby having a disadvantageous effect on less aciduric oral streptococci, such as *S. sanguinis*, but would also increase their sensitivity to the effects of low pH, helping *S. mutans* to become more dominant (Dashper and Reynolds, 2000). ③ Plasmid transfer exists among different co-cultured *Streptococcus*. In mixed cultures of *S. mutans* and *S. gordonii* harbouring a shuttle plasmid, the transfer of plasmid DNA from *S. gordonii* to *S. mutans* was observed in a CSP and mutacin IV-dependent manner. *S. mutans* may utilize the competence-induced bacteriocin production to acquire transforming DNA from other species living in the same ecological niche (Kreth et al., 2005). ④ The effects of other species of oral bacteria on virulence gene expression by *S. mutans* had been studied. As compared to mono-species biofilms, biofilm formation by *S. mutans* was significantly decreased when grown with *S. sanguinis*, but was modestly increased when co-cultivated with *Lactobacillus casei*. Together with the formation of biofilms of lactobacillus, streptococcus part of the virulence factor expression *spaP* *gtfB* *gbpB* reduced, and the common oral *S. mutans* biofilm formation and *gbpB* *spaP* also reduced the *gtfB* did not fall (Wen et al., 2010). ⑤ Effect of pH on the lactate dehydrogenase genes expression of *S. mutans*. The acidogenicity and growth of *S. mutans* isolates were affected by the growth condition. The *ldh* expression was upregulated when *S. mutans* was cultured under acidic environment to survive in hostile environment and maintain its cariogenicity (Pi et al., 2010).

Prospect

In future, the study of non-mutans streptococci collected and isolated from teeth diagnosed as high and low active caries subjects would be conducted to provide some evidence for the hypothesis, which cariogenic microorganisms or acid produced by bacteria may have affect on the virulence properties of non-mutans streptococci, for example inducing an increase of acid produce. Suppression Subtractive Hybridization (SSH) technique may be used to analyze gene expression of non-mutans streptococci isolated from high and low active caries subjects. And comparative analysis of virulence of the strains would be conducted by routine biochemical method. Analysis of non-mutans streptococci virulence may provide some gene expression and biochemical evidence for the hypothesis.

Nowadays, along with the development of science research and new technology, people are paying much more attention on what those bacteria in oral cavity are doing than which kind of bacteria contributes to this disease. Paying attention to the role of non-mutans streptococci in the progression of dental caries may advance knowledge of pathology and etiology of caries and offer additional approaches for the prevention and therapy of dental caries. The daily use of oral care products might be very important strategies to neutralize the mouth and keep the pH within healthy ranges, and to prevent caries and control the caries process.

ACKNOWLEDGEMENT

This work was supported by a grant from the Science and Technology Commission of Shanghai, Shanghai, People's Republic of China (grant no. 08DZ2271100), and the Shanghai Leading Academic Discipline Project, Shanghai, People's Republic of China (Project number: S30206). The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

- Aas JA, Griffen AL, Dardis SR, Lee AM, Olsen I, Dewhirst FE, Leys EJ, Paster BJ (2008). Bacteria of dental caries in primary and permanent teeth in children and young adults. *J. Clin. Microbiol.* Apr;46(4):1407-17.
- Ashby MT, Kreth J, Soundarajan M, Sivuilu LS (2009). Influence of a model human defensive peroxidase system on oral Streptococcal antagonism. *Microbiol.*; 155(Pt 11): 3691-700.
- Dashper SG, Reynolds EC (2000). Effects of organic acid anions on growth, glycolysis, and intracellular pH of oral streptococci. *J. Dent. Res.*; 79(1): 90-6.
- Fejerskov O, Kidd E (eds) (2008). *Dental caries: The disease and its clinical management*. 2nd ed. Oxford: Blackwell Munksgaard; p. 287-323.
- Hojo K, Nagaoka S, Ohshima T, Maeda N (2009). Bacterial interactions in dental biofilm development. *J. Dent. Res.*; 88(11): 982-90.
- In-Geol Choi, Sung-Hou Kim (2007). Global extent of horizontal gene transfer. *PNAS*; 104(11): 4489-4494.
- Kolenbrander PE, Andersen RN, Blehert DS, Eglund PG, Foster JS, Palmer RJ (2002). Communication among oral bacteria. *Microbiol. Molec. Biol. Rev.*, 66: 486-505.
- Kreth J, Merritt J, Shi W, Qi F (2005). Competition and coexistence between *Streptococcus mutans* and *Streptococcus sanguinis* in the dental biofilm. *J. Bacteriol.*; 187(21): 7193-203.
- Kreth J, Merritt J, Shi W, Qi F (2005). Co-ordinated bacteriocin production and competence development: a possible mechanism for taking up DNA from neighbouring species. *Mol. Microbiol.*; 57:392-404.
- Kreth J, Vu H, Zhang Y, Herzberg MC (2009). Characterization of hydrogen peroxide-induced DNA release by *Streptococcus sanguinis* and *Streptococcus gordonii*. *J. Bacteriol.*; 191(20): 6281-91.
- Kreth J, Zhang Y, Herzberg MC (2008). Streptococcal antagonism in oral biofilms: *Streptococcus sanguinis* and *Streptococcus gordonii* interference with *Streptococcus mutans*. *J. Bacteriol.*; 190(13): 4632-40.
- Loesche WJ (1979). Clinical and microbiological aspects of chemotherapeutic agents used according to the specific plaque hypothesis. *J. Dent. Res.*; 58: 2404-2412.
- Marsh PD (1994). Microbial ecology of dental plaque and its significance in health and disease. *Adv Dent Res*; 8: 263-271.
- Marsh PD (2006). Dental plaque as a biofilm and a microbial community - implications for health and disease. *BMC Oral Health*. 15; 6 Suppl 1: S14.
- ÓSullivan JM, Jenkinson HF, Cannon RD (2000). Adhesion of *Candida albicans* to oral streptococci is promoted by selective adsorption of salivary proteins to the streptococcal cell surface. *Microbiol.*; 146: 41-48.
- Pi G, Liu T, Yang J, Jiang Y (2010). Effect of pH on the Lactate Dehydrogenase Gene Expression of *Streptococcus mutans*. *SCIENCEPAPER ONLINE* 2010-11-22, <http://www.paper.edu.cn>1-6.
- Takahashi N, Nyvad B (2008). Caries ecology revisited: microbial dynamics and the caries process. *Caries Res.*; 42: 409-18.
- Takahashi N, Nyvad B (2010). The Role of Bacteria in the Caries Process: Ecological Perspectives. *J. Dent. Res. Oct 5*. [Epub ahead of print].
- Takahashi N, Nyvad B (2011). The role of bacteria in the caries process: ecological perspectives. *J. Dent. Res.*; 90(3): 294-303.
- Takahashi N, Yamada T (1999). Acid-induced acidogenicity and acid tolerance of non-mutans streptococci. *Oral Microbiol. Immunol.*; 14: 43-48.
- Wang BY, Chi B, Kuramitsu HK (2002). Genetic exchange between *Treponema denticola* and *Streptococcus gordonii* in biofilms. *Oral Microbiol. Immunol.*; 17(2): 108-12.
- Wang BY, Deutch A, Hong J, Kuramitsu H (2010). Proteases of an Early Colonizer Can Hinder *Streptococcus mutans* Colonization in vitro. *J. Dent. Res. Nov 18*. Epub ahead of print.
- Wen ZT, Yates D, Ahn SJ, Burne RA (2010). Biofilm formation and virulence expression by *Streptococcus mutans* are altered when grown in dual-species model. *BMC Microbiol.*; 14;10:111.
- Zheng L, Chen Z, Itzek A, Ashby M, Kreth J (2010). Catabolite Control Protein A (CcpA) Controls Hydrogen Peroxide Production and Cell Death in *Streptococcus sanguinis*. *J. Bacteriol. Oct 29*. [Epub ahead of print].