

Immunological aspects of dental caries

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Abstract

The relations between host and bacteria present in oral cavity are dynamic and subject to many conditions. Microorganisms present in the oral cavity are not enough to cause a disease. Potentially pathogenic bacteria can be isolated from clinically healthy volunteers. Biological balance, called homeostasis, is of primary importance. Thus a crucial role plays immune response to bacterial infection. It has been stated over 100 years ago that caries is caused by bacteria. And yet both *Streptococcus mutans* and *Lactobacillus* spp. permanently colonize oral cavity. In fact, they belong to natural oral microflora. The studies on immunological aspects of caries have been conducted for many years now. They include various mechanisms. One of the most studied aspects is the immunoglobulin level. The results of the studies concerning correlation between serum or salivary immunoglobulin level and caries advancement are equivocal. Much hope is placed in studies on glucosyltransferases (GTF): bacterial enzymes, converting sucrose into glucans – extracellular polysaccharides, actively taking part in cellular adhesion in microbial biofilm forming process. Main elements of caries prevention comprise mechanical dental plaque removal by means of effective brushing, as well as limitation of daily sugar intake.

Key words: dental caries, *Streptococcus mutans*, host response, glucosyltransferases.

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Human oral cavity is colonized by about 300 to 500 microorganism species. Most of them comprise commensal and opportunistic bacteria. The relations between host (human organism) and bacteria present in oral cavity are dynamic and subject to many conditions. They are representative of the virulent capability and properties of bacteria as well as defensive forces of the host. Bacteria colonizing oral cavity are believed to be the cause of various systemic diseases. The most studied example is Gram-positive bacteria: *Streptococcus sanguis* and *Streptococcus oralis*, that can lead to bacterial endocarditis. Periopathogenic bacteria, such as *Actinobacillus actinomycetemcomitans* and other anaerobic rods, can lead to ischemic heart disease [1]. Some of the bacteria inhabiting oral cavity can only be isolated in specific moments, sometimes really rarely. Most of them reside in dental plaque. Microorganisms synthesize specific antigens, that are recognized by host as foreign and thus provoke immune response of the organism. It is still not fully elucidated what does really protect human organism from bacterial invasion and disease progression. Homeostatic control of a multicellular organism, such as a human body, depends first of all on integrated function of single cells. Thus a great role play

efficiency of informative systems of human body, as well as information transfer from local area to the remote regions of human organism. The entire body is subjected first of all to the hormonal regulation, while the regional and local areas are under control of so called “cytokine networks”. Cytokines can be produced by various cell types. Their synthesis can be induced by many stimulants: bacterial lipopolysaccharides (LPS), structural proteins of bacterial cell walls, carbohydrates, lipoproteins and many other small molecules. Bacteria are known to stimulate synthesis of both pro-inflammatory and anti-inflammatory cytokines.

Microorganisms present in the oral cavity are not enough to cause a disease. Potentially pathogenic bacteria can be isolated from clinically healthy volunteers. Biological balance, called homeostasis, is of primary importance. Thus a crucial role plays immune response to bacterial infection. It has been stated over 100 years ago that caries is caused by bacteria. And yet both *Streptococcus mutans* and *Lactobacillus* spp. permanently colonize oral cavity. In fact, they belong to natural oral microflora. As long as cariogenic bacteria are not infrequent guests in oral cavity, caries cannot be considered an exogenous bacterial condition, but rather a result of ecological aberrations. Cario-

genic bacteria exist in harmony with their environment. Integrity of oral mucosa and enamel surface presents physical barrier against microorganisms and high-molecular-weight antigens penetration, thus contributing to healthy oral cavity. It is only after immunological breakdown or disruption of the bodily homeostasis that a tooth disease (dental caries) begins. An important role in oral homeostasis and caries prevention plays saliva with its components [2]. The defensive mechanisms of saliva comprise specific and non-specific factors. The non-specific factors include first of all lysozymes, lactoferrin and apolactoferrin, peroxidases as well as mucins and agglutinins. Lysozyme is the main element of non-specific defensive system: lysozyme-protease-inorganic monovalent anion (bicarbonates, fluorides, chlorides, thiocyanates), that leads to bacterial cells lysis by means of hydrolysis of peptidoglycan – the building material of bacterial cell wall. Lactoferrin as well as apolactoferrin destroy bacterial cells, mainly *Streptococcus mutans*. Sialoperoxidase system leads to synthesis of hypothiocyanite and/or hypothiocyanous acid, thus impairing bacterial metabolism by glycolysis inhibition. Histatins (histidine-rich proteins) exhibit strong activity against microorganisms, especially bacteria and fungi, as well as inhibit development and kill *Streptococcus mutans* and *Candida albicans*. Mucins and agglutinins take up bacteria, leading to their agglutination and aggregation. Also physical removal of microorganisms by constant salivary flow is of much importance. Another group of defensive salivary components is specific factors. This group comprises intra-epithelial lymphocytes (a natural barrier for bacterial antigens), Langerhans cells (blocking bacterial metabolism), as well as complement system, activating neutrophils, that phagocyte microorganisms, together with monocytes/macrophages. Still the most important element appears to be antibodies of class immunoglobulin G (IgG), IgA and IgM, that block bacterial metabolism and neutralize microorganisms. A dominating immunoglobulin is secretory IgA (sIgA) – the main immunoglobulin of saliva. The sIgA is secreted by all the salivary glands. It is an extremely important element of antibacterial, antiviral as well as antifungal defense of human body.

The studies on immunological aspects of caries have been conducted for many years now. They include various mechanisms [3-7]. One of the most studied aspects is the immunoglobulin level. It has been stated by many authors, that caries provokes humoral immune response [8-10]. One of the concepts of immunological anticariotic regulation assumes that the immunoglobulins are induced by ingestion of saliva comprising antigenic determinants of *Streptococcus mutans*. And yet the proper assessment of salivary or peripheral serum immunoglobulins against cariogenic microorganisms is rather difficult, as long as there is high risk of interactions between different antibacterial proteins. Moreover the source of these antibodies could be gingival fluid, while specific anti-*Streptococcus mutans* immuno-

globulin A (sIgA) level can vary depending on the infection duration and localization [11]. In children suffering from leukemia and treated with cytostatics the serum neutrophils level was found to be decreased and significantly correlate with increased cariogenic bacteria level in the saliva [12]. On the other hand, neither increase of cariogenic bacteria nor exacerbation of caries intensity was observed in case of decreased immunoglobulin level in peripheral serum in hypogammaglobulinemia [13]. The results of the studies concerning correlation between serum or salivary immunoglobulin level and caries advancement are equivocal [14]. In a survey on the schoolchildren a statistically significant, positive correlation has been observed between caries process advancement and increased salivary and serum IgA activity. No significant correlation has been stated between IgG and IgM level and caries intensity index [15]. This observation reflects local response to the antigen stimulation by cariogenic bacteria. Immunoglobulin A is the predominant immunoglobulin in oral mucous membrane secretion fluids. Immunoglobulin G on the other hand is only synthesized in small amounts by the secretory epithelial cells of salivary glands. The IgG presence in saliva results mainly from serous “leakage” through the sulcular epithelium. Immunoglobulin M is similarly synthesized selectively by the parotid gland. The results of the other studies do not support the correlation between serum or salivary immunoglobulin level and caries advancement [16, 17].

The subsequent studies proved a positive, statistically significant correlation between caries progression and bacteria (namely *Streptococcus mutans* and *Lactobacillus* spp.) as well as specific anti-*Streptococcus mutans* IgG immunoglobulin salivary level [18]. On the grounds of IgG, IgA and IgM salivary level, as well as puwp value and childhood diseases morbidity it has been stated that the children frequently falling sick do also exhibit higher caries intensity, increased salivary IgG and IgM level and decreased salivary IgA level [19].

The studies on immunological mechanisms and the role they play in caries development and course have led to designation of *Streptococcus mutans* antigen responsible for bacteria adhesion to the tooth surface, known as SAI II [20]. Fimbriae surrounding *Streptococcus mutans* cell, allowing for cell adherence to substrate, have been found to lead to the increase of salivary IgA, suggesting that they can behave as antigens, thus exerting anti-cariogenic effect [21].

The caries vaccine has been object of much interest [22-27]. Antigenic structure of *Streptococcus mutans* bacteria has been described in great detail. Nevertheless, no efficient caries vaccine has been developed to date. One of the main reasons is serious adverse events observed in laboratory animals, notwithstanding the huge expenditures and many scientists' efforts. Another impediment that must be faced in caries vaccine development process is lack of immunological memory of sIgA. Despite these difficulties the studies are continued and their results seem very interesting.

Much hope is placed in studies on glucosyltransferases (GTF): bacterial enzymes, converting sucrose into glucans – extracellular polysaccharides, actively taking part in cellular adhesion in microbial biofilm forming process [28, 29]. Rat immunization by means of GTF containing vaccine has led to increase of salivary IgA concentration and significant ($P < 0.05$) decrease in caries incidence [30].

Laboratory rats were also immunized by administration of a vaccine containing fragment of antibody against *Lactobacillus* (scFv). This antibody recognized *Streptococcus mutans* antigens (SAI II) leading to the agglutination of bacterial cells and thus to decrease in *Streptococcus mutans* as well as in caries reduction [31]. The aim of another study was to assess the effectiveness of oral rinsing with special milk from cows immunized with antigens of *Streptococcus mutans* cell wall. As a result, a significant inhibition of saliva and dental plaque recolonization by *Streptococcus mutans* group was obtained [32]. By means of monoclonal technique more safe synthetic antibodies were also obtained [33]. And yet all the above mentioned vaccines only provide passive immunization.

The defensive capabilities of each organism are genetically determined. They can only be affected by genetic and polymorphic mutations. Whether we fall ill or not is foredoomed to some extent and cannot be influenced. Everything is written down in the given nucleotides sequence. Our response to infection is encoded in the nuclear DNA. Perhaps the prodigious progress in basic sciences will enable us to prevent diseases, such as caries, by means of innovative genetic engineering techniques, such as gene transfer directly to the specific cells. But for now we must remember, that the main elements of caries prevention comprise mechanical dental plaque removal by means of effective brushing, as well as limitation of daily sugar intake.

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