

RECENT ADVANCES IN PERIODONTOLOGY

Andrej Aurer

Department for Periodontics, School of Dental Medicine,
University of Zagreb, Zagreb, Croatia

Summary

Available information on periodontal diseases are numerous, ambiguous and for the most part highly specialised.

Through the years most of the research was focused on the microbiological aspects of the periodontitis. It has been noticed that bacteria alone are not sufficient for the initiation of periodontal diseases, although they play an important part in the process. Host response, smoking, stress and other risk factors influence the appearance of the disease, and the susceptibility to aggressive forms of periodontitis is genetically determined.

This knowledge brought significant changes to the concept of etiology, prevention and the treatment of periodontal diseases.

There is a huge amount of data on the bacterial role in the initiation of periodontal pockets, changes in the junctional epithelium, destruction of periodontal ligament and resorption of the alveolar bone. The bacteria play an indirect role in the tissue destruction, through activation of the host response which becomes pathological. It seems hard to believe that the same host response factors are responsible both for the defence, as well as the appearance of the disease. Therefore one of the basic questions that can be asked today is why isn't the periodontal disease self-limiting in its nature, or why doesn't it stop spontaneously.

The studies done in the last years are trying to explain this phenomenon by means of molecular and cellular regulatory mechanisms.

The studies using multi-variate analysis indicate that the bacterial components participate in the disease expression with a relatively low percentage. Host response factors are at least as, if not more important in the initiation of periodontitis. The complex interaction of the bacterial challenge and native and acquired immunity determine the final outcome of the disease.

Progress in understanding the molecular basics of the disease in the last decade has led to a better understanding of the process of the disease.

Key words: periodontitis; oral microbiome; host response; immunomodulation.

INTRODUCTION

Available information on periodontal diseases are numerous, ambiguous and for the most part highly specialised. Through the years most of the research was focused on the microbiological aspects of the periodontitis. It has been noticed that bacteria alone are not sufficient for the initiation of periodontal diseases, although they play an important part in the process. Host response, smoking, stress and other risk factors influence the appearance of the disease, and the susceptibility to aggressive forms of periodontitis is genetically determined. This knowledge brought significant changes to the concept of etiology, prevention and the treatment of periodontal diseases.

RECENT ADVANCES IN PERIODONTOLOGY

Periodontal diseases, including gingivitis and periodontitis, are the most commonly occurring, yet very specific infections, due to the unique anatomical features of periodontal structures and the nature of pathogenic plaque biofilm disease. Periodontitis remains a major cause of tooth loss in adults, and presents a major public health problem worldwide [1]. Periodontal diseases not only significantly affect oral health, but are increasingly recognised as serious infections with profound effects on general health in association with systemic diseases and disorders, such as cardiovascular diseases, cerebral stroke, diabetes, preterm birth and aspiration pneumonia [2-4]. Systemic diseases associated with oral biofilm belong to the group of diseases that present highest costs of treatment for the public health, which is another important factor contributing to the importance of proper understanding of etiology and progression of periodontal diseases and their prevention which has great value for oral and general health [5].

Over the past years, most of the research was focused on the microbiological aspects of the periodontitis. It has been noticed that bacteria alone are not sufficient for the initiation of periodontal diseases, although they play an important role in the process. Host response, smoking, stress and other risk factors influence the presence of disease, and the susceptibility to aggressive periodontitis is genetically determined [6,7].

The bacteria play an indirect role in the tissue destruction, through activation of the host response which becomes pathological. It seems hard to believe that the same host response factors are responsible both for the defence, as well as the appearance of the disease. Therefore one of the basic questions that can be asked today is why isn't the periodontal disease self-limiting in its nature, or why doesn't it stop spontaneously.

Substantial progress has been achieved in understanding the etiology and pathogenesis of periodontal diseases, including recognition of dental plaque as biofilms, appreciation of the importance of host-microbe symbiosis, and understanding of the crucial role of host susceptibility in initiation and development of diseases, as well as great importance of innate immunity in the maintenance of periodontal homeostasis. We will give a brief account of the current scientific concepts of plaque biofilms, host response and host-biofilm interactions, as well as new therapeutic strategies.

It is estimated that at least 10^{14} bacterial commensals of various species reside on the surface of skin, teeth, dentures, the mucosal epithelial lining of the respiratory, gastrointestinal and urinary tracts. Bacteria form about 90% of all cells in our organisms, and their mass is calculated at 1-2 kilograms of the full body weight. What amazes is the fact that most of these bacteria, and bacterial interactions with the host are not pathogenic in nature and do not activate the immune system [8]. It has been shown that a large number of oral bacterial species are not detectable using traditional culture methods.

Last couple of years, new methods of sequencing whole microbial communities using 16s ribosomal RNA, called „high-throughput methods“ were developed [9]. They allow for the sequencing of whole genomes of specific bacteria, or identification and sequencing of completely unknown phyla or species, as well as study of complete genomes and metabolic activities of complete microbial communities [10]. They can be used to discover gene activations responsible for bacterial pathogenicity. Genomic sequencing has revealed extreme variability of clone genomes in any given species, which stresses the importance of individual genes encoding virulence factors, and not only the presence and levels of certain species [11].

Predominant Gram positive bacteria were consistently found, not Gram negative like the numerous textbooks claim. The mistake stems from earliest studies, as later has been shown that mature Gram positive bacteria colour variably or negative [12].

Periodontitis has a polymicrobial etiology within the framework of a complex microbial ecosystem. With advances in sequencing technologies, comprehensive studies to elucidate bacterial community differences have recently become possible. 81% of sequences could be mapped to cultivated species.

Human Oral Microbiome Genome Project was started in 2009. The goal is sequencing of the complete genetic code. Gram positive bacteria are predominant. Around 700 species and 35000 clones were found. Huge number of bacterial species are not native to oral cavity (thousands). Even methanogenic members of Archaea domain were found. Most of the oral bacteria belong to the following 11 phyla: Ac-

tinobacteria, Bacteroidetes, Chloroflexi, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, Synergistetes, Tenericutes and unnamed TM7 and SR11. Members of Firmicutes are the most frequent bacteria and include streptococci [8].

Kumar et al. [13] analysed the differences between health- and periodontitis-associated bacterial communities, and analysis showed distinct community profiles in health and disease. Community diversity was higher in disease, and 123 species were identified that were significantly more abundant in disease, and 53 in health. Spirochaetes, Synergistetes and Bacteroidetes were more abundant in disease, whereas the Proteobacteria were found at higher levels in healthy controls. Within the phylum Firmicutes, the class Bacilli was health-associated, whereas the Clostridia, Negativicutes and Erysipelotrichia were associated with disease. Elucidation of these differences in community composition provides a basis for further understanding the pathogenesis of periodontitis.

In another study the peri-implant microbiome was shown to differ significantly from the periodontal community in both health and disease. Peri-implantitis is a microbially heterogeneous infection with predominantly gram-negative species, and is less complex than periodontitis [14].

Significant association with periodontitis was found for Synergistetes (Deferribacteres) D084 i BH017, Bacteroidetes AU126, Division SR1 (OP11) X112, Division TM7 I025 and known species *Anaeroglobus geminatus*, *Eubacterium saphenum*, *P. endodontalis*, *P. denticola* and *Cryptobacterium curtum*. With *P. gingivalis*, *T. denticola* and *T. forsythia*, *P. tanneriae*, *F. alocis* and *P. endodontalis* were related with the disease [15]. New molecular ecology techniques have widened the scope of knowledge of subgingival species and possible importance of uncultivable bacteria.

The studies using multi-variate analysis indicate that the bacterial components participate in the disease expression with a relatively low percentage. Host response factors are at least as, if not more important in the initiation of periodontitis [16]. The complex interaction of the bacterial challenge and native and acquired immunity determine the final outcome of the disease.

Progress in appreciating the molecular basics of the disease in the last decade has led to a better understanding of the disease process.

Genetic susceptibility to aggressive and chronic forms of periodontitis is well known. Studies on families have shown the prevalence of familial aggregation to be 40-50%, while in some families the prevalence was found to be up to 65% [17]. Several genetic predispositions for development/more severe disease were discovered [18]. According to studies on twins, 38-82% of disease variance is due to genetic factors [19], while the specific bacterial components are responsible for 9-16% of variance in periodontitis.

Consensus of the 7th European Workshop on Periodontology that took place last year had following conclusions. Current preventive and treatment approaches are only partially effective, and this appears due to the therapeutic focus remaining primarily upon biofilm management rather than embracing a pivotal role for inflammation as a driver of biofilm composition as well as tissue damage [20].

Periodontitis remains a major public health issue and current management approaches have failed to impact upon the most high-risk proportion of the population and those with the most severe disease.

There is a need to develop new, more effective, and efficient preventive and treatment approaches for gingivitis and periodontitis, which embrace recent advances in understanding of host modulation and inflammation resolution, as well as direct management of the microbiota.

Focus is maintained on the development of new therapeutic approaches, based on the understanding of host response modulation and resolution of disease, as well as on the direct access to microbial community [21].

Neutrophils are main cells of the innate immunity. They are responsible for the phagocytosis of microorganisms, form a protective wall stopping invasion of bacteria under the pocket epithelium. It was considered that abnormal function which leads to wrong inflammatory response is the central mechanism of disease progression, or that hyperactive neutrophil is the agent of destruction. Now it seems that normally activated neutrophils accumulate and persist in the tissues, without being able to resolve bacterial invasion and lead to tissue destruction [22]. Sophisticated approach would aim at promoting the inflammation resolution by inducing apoptosis of neutrophils in the periodontium. The goal is to find substances that can limit the tissue destruction, but without impairment of the antimicrobial activity. Last years natural lipid agonists, resolvins, were linked to active induction of persistent inflammation resolution and lead to disappearance of clinical inflammation. Neucalcin, new molecule blocks TNF α induced raised levels of intracellular calcium, but does not block degranulation or activation after bacterial phagocytosis or influence bactericidal activity [23]. Although precise mode of action is unknown, such approaches that differentiate inflammation from bactericidal activity can lead to development of new therapeutics for controlling the pathways of persistent periodontal inflammation [24].

Obesity influences innate and acquired immune response, and is characterised by changed systemic inflammatory response brought by disbalance in the cytokine network, raised levels of acute phase proteins and proinflammatory cytokines, like tumor necrosis factor and leukocytes in the plasma of obese persons [25,26]. If a hyperinflammatory state exists in the alimenatry induced obesity remains controversial [27]. Obesity in clinical studies is linked to periodontitis [28,29].

Obesity raises the susceptibility to infection and postoperative complications [30]. It seems that high lipid diet disrupts normal immune response to *P. gingivalis*. Repeated *P. gingivalis* bacteraemias result in repeated endothelial/macrophage invasion which causes chronic inflammatory state, exacerbates atherosclerosis and periodontitis through homotolerance induction [31]. Tolerance induction is responsible for the role of obesity in the faster progression of periodontal diseases [32].

The aim of immune host response modulation is to achieve clinical benefits out of understanding the host response mechanisms. New concepts in the treatment make use of natural pathways for inflammation inhibition as well as activation of healing and regeneration. Inhibition or modification of inflammatory/immune response is strived for, using different mechanisms implementing substances like antimicrobial peptides, probiotics, antiinflammatory lipid mediators and micronutrients [33]. Good example of a succesful immunomodulatory implementation is treatment of rheumatoid arthritis, where targeted inhibition of inflammatory mediators led to succesful development of several therapeutics [34].

A variety of treatment strategies have been developed to target the host response to periodontal infection. Matrix metalloproteinase inhibitors, such as low-dose formulations of doxycycline, have been used in combination with scaling and root planing or surgical therapy. In addition, high-risk patient populations, such as patients with diabetes, have benefited from systemic matrix metalloproteinase administration. Encouraging results have been shown using soluble antagonists of tumor necrosis factor and interleukin-1 delivered locally to periodontal tissues in non-human primates, as well as more recent evidence using gene therapy vectors to provide a longer-term delivery of receptor antagonists at the periodontium [35,36].

Other therapeutic strategies being explored are aimed at inhibiting signal transduction pathways involved in inflammation. Pharmacological inhibitors of NF- κ B and p38 MAPK pathways are actively being developed to manage rheumatoid arthritis and inflammatory bone diseases. Using this novel strategy, inflammatory mediators, including pro-inflammatory cytokines (interleukin-1, tumor necrosis factor, interleukin-6), matrix metalloproteinases and others, would be inhibited at the level of cell-signaling pathways required for transcription factor activation necessary for inflammatory gene expression [37]. These therapies may provide the next generation of disease-specific chemotherapeutics to manage chronic periodontitis. Currently developed therapeutics have a significant, albeit clinically rather limited effect [38].

Resolution of iflammation can be understood as a stop for inflammatory signaling processes. Disturbance of inflammation resolution, with overactivation of inflammatory response, plays a role in initiation and progression of periodontal de-

struction. Proresolving lipid mediators have been described: lipoxins and resolvins. Diseases like periodontitis, asthma or rheumatoid arthritis have similar pathogenic mechanisms, with the constant activation of chronic processes that finally leads to tissue destruction [39].

In fact, new data suggest that the inflammatory response (gingivitis) might actually precede the emergence and overgrowth of periodontal pathogens in the biofilm. Moreover, new data suggest that failure of resolution of inflammation pathways may play as important a role in disease as overproduction of proinflammatory mediators.

Experiments in animals and humans suggest an exciting new approach to the pharmacologic modulation of inflammation in disease: the use of receptor agonists of resolution of inflammation to actively regulate the inflammatory response. The same lipid mediators that drive resolution of inflammation enhance microbial clearance at mucosal surfaces and improve bacterial clearance in infection [40].

In addition, the use of lipoxins has demonstrated significant potential in the management of host response to periodontitis [40]. Docosahexaenoic acid is example of such a molecule, whose action has been confirmed in experimental studies.

Use of live probiotic cultures for propagation of healthy microflora is a relatively new concept. There is evidence that probiotics can influence the composition of microflora, and to a lesser degree the outcome of periodontal therapy [41]. It seems that the action is temporary, or continuous administration is needed for the effect to remain long-term. The data point to possibility of manipulation of oral microflora, or to a lesser degree periodontal health, either through direct microbial interactions, or by immunomodulatory interactions.

Due to limited value of available studies, it is difficult to confirm clinical importance of such statistically significant findings. Another question is should specific oral probiotics be developed for use, or the general probiotics suffice. Effects of probiotic bacteria on the periodontal condition (plaque index, gingivitis index, bleeding on probing, PPD) are much more limited in magnitude when compared with the studies reporting on microbiological outcomes [41].

Nutritional modulation of periodontal inflammation is still at an early stage and relatively little is known about the influence of micronutrients on the progression of disease or response to therapy. It is known that high calorie intake induces inflammation [42], and obesity is linked to periodontitis [43]. Raised sugar intake increases gingival bleeding, and lowered intake of antioxidants and omega-3 fatty acids raises the disease prevalence [44]. The plasma of patients with periodontitis showed lowered levels of vitamins C, D, calcium and magnesium. Potentially beneficial influence of additional nutritional therapeutical approaches by supplement-

ting vitamins C and D, omega-3 fatty acids, Ca and Mg and lowering the sugar intake [45,46].

CONCLUSION

Advanced microbiological methods will offer a clearer understanding of the bio-film functioning as an ecosystem and help identify new periodontal pathogens. The knowledge of host response and modifying factors can help in the future treatment of periodontal diseases and development of new preventive measures. Further developments of biological approaches in the periodontal therapy are expected.

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Sažetak

Suvremene spoznaje o parodontnim bolestima

Dostupne informacije o parodontitisu su raznovrsne, brojne i velikim dijelom visoko specijalizirane.

Tijekom godina većina istraživanja bila je usmjerena na infekcijski aspekt parodontitisa. Uočeno je da bakterije nisu dostatne, iako su bitne u nastanku parodontitisa. Obrambene snage organizma, pušenje, stres i drugi faktori rizika bitno utječu na pojavu bolesti, pri čemu je genetski determinirana sklonost za agresivne oblike parodontitisa.

Ove spoznaje dovele su do značajnih promjena u koncepciji etiologije, prevencije i liječenja parodontnih bolesti.

Veliki je broj podataka o tome kako bakterije djeluju na nastanak parodontnih džepova, promjenu spojnog epitela, destrukciju ligamenata i resorpciju alveolne kosti. Razaranje tkiva bakterije izazivaju indirektno, aktiviranjem faktora obrane domaćina, čije djelovanje postaje patološko. Čini se nevjerojatnim da isti faktori domaćina uzrokuju obranu, ali i pojavu bolesti. Stoga je pitanje, zašto se proces parodontne bolesti spontano ne zaustavi, jedno od temeljnih pitanja, koje danas postavljamo i na koje valja odgovoriti.

Istraživanja vršena posljednjih godina pokušavaju pomoću molekularnih i staničnih regulacijskih mehanizama objasniti ovaj fenomen.

Studije prilagođene multivarijantnim analizama pokazuju da bakterijske komponente sudjeluju u ispoljavanju bolesti u relativno malom postotku. Faktori domaćina su jednako, ako ne i više značajni u nastanku parodontitisa. Kompleksna interakcija bakterijskog izazova, te prirođeni i stečeni faktori domaćina determiniraju konačni ishod bolesti.

Napredak u poznavanju molekularnih osnova bolesti u posljednjem je desetljeću doveo do boljeg razumijevanja procesa bolesti.

Ključne riječi: periodontitis; oral microbiome; host response; immunomodulation.

Corresponding author:
Andrej Aurer
e-amil: aurer@sfzg.hr