THE ECOLOGICAL CATASTROPHE OF ORAL DISEASES:
A POSSIBLE LINK BETWEEN PERIODONTITIS AND PROTOZOA

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Periodontal disease (PD) is one of the prevalent diseases in the adult population. The etiology of PD has never been completely understood, however, loss of balance between the host immune system and the microbial virulence of PD pathogens may be considered the trigger of PD. In fact, the immune system, activated by microbiological agents, attacks the host and not the biofilm bacteria, causing the destruction of periodontal tissue, alveolar bone and loss of teeth. Parasites may play an important role in the pathology of PD. The first studied and the most common parasite in the oral cavity is Entamoeba gingivalis. A possible link between E. gingivalis and PD has never been demonstrated completely, however E. gingivalis is infrequently found in people without PD. In addition, there is evidence that E. gingivalis could favour the onset and progression of PD. In conclusion, we can assert that E. gingivalis and PD may be correlated. This relationship can open new therapeutic approaches for treating PD, particularly in cases refractory to therapy.

Periodontal disease (PD) is one of the most prevalent diseases in the adult population and manifests itself with the classical symptom triad: tooth mobility, foetor ex ore, and gingival bleeding. PD is characterized by loss of connective tissue attachment to the tooth, and pathological migration of the junctional epithelium apically, which leads to pocket formation, tooth mobility, and finally tooth loss. There are different types of PD, but the most common is chronic periodontitis. The pathogenesis of PD is multifactorial and bacteria have a prominent role (1). There is ample evidence supporting the microbial aetiology of PD. Smoking, alcohol consumption, and systemic conditions such as diabetes, osteoporosis, malnutrition and stress are considered relevant risk factors. Recently, it was observed that PD appears to increase the risk of cardiovascular disease, pulmonary disease, preterm and low birth weight.

Pathology of periodontal disease

In the oral cavity, bacteria are structured as dense aggregates, attached to enamel surface, called biofilms (2, 3). Under certain conditions, biofilm could alter its composition and may cause disease (4, 5). Dental plaque and microflora colonizing gingival pockets can promote inflammation of the adjacent host gingival tissues. The epithelial cells of gingival sulcus are the first line of defence against the plaque bacteria (6).

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Dental plaque is structured as a complex polymicrobial biofilm (6, 7). In the progression of PD, this biofilm changes from Gram-positive facultative anaerobes to Gram-negative anaerobic bacteria (8). The accumulation of dental plaque causes inflammation in the adjacent gingival sulcus extending biofilm in the deepest part of sulcus itself, creating a deeper pocket and favouring the growth of anaerobes, such as *Spirochetes* and *Bacteriodetes* (7).

Innate immune responses in periodontal tissues are stimulated by Gram-negative periodontal bacteria, among which the most aggressive have been identified as the “red complex” group: *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. These microbes are highly virulent and neutralize host defences, causing PD. However, only a limited number of individuals with red complex species develops PD, suggesting a complex multifactorial aetiology of this disease, involving loss of balance between bacteria virulence and the innate immune system.

The immune system

Loss of balance between the host immune system and the microbial virulence may be considered the trigger of PD. In PD, the persistently activated immune system, triggered by microbiological agents, damages the host tissues with little effect on the biofilm bacteria, causing a progressive destruction of periodontal tissue, alveolar bone and teeth loss. This process is related to the severity of PD, modulating responses of immunity to oral biofilm, leading to dysregulation of innate immunity (8). It is also known that immune dysregulation is associated not only with PD, but also with other numerous systemic diseases such as cardiovascular disease, obesity, pulmonary disease, etc. In fact, the interactions between microbial virulence factors and the immune system have been largely investigated in regard to the aetiology of PD. Recent genetic and molecular studies have described the relationship between bacterial virulence and host immune response and the pathways involved in PD progression (9-18).

A possible link between protozoa and PD

Protozoa could play an important role in the pathology of PD. The first studied and the most common parasite in the oral cavity is *E. gingivalis*.

The first description of *E. gingivalis* in the mouth was given by G. Gros in 1849 (19). Subsequently, Lyons and colleagues detected *E. gingivalis* in periodontal pockets, but not in healthy sites (20). Basing on the idea that *E. gingivalis* was involved in the pathogenesis of PD, they tried a new protocol based on oxygen peroxide and metronidazole that, even recently, demonstrated to be effective (21, 22). This idea was firstly contrasted for difficulties in molecular identification of the parasite.

Recently, an *in vitro* experiment explained a host-protozoa relationship. Human cell line cultures were challenged with putative pathogenic PD bacteria in the planktonic state, i.e., a cell suspension in growth media or buffered solutions, evidencing that *in vitro* experiments are far disconnected from *in vivo* conditions. In fact, *in vitro* studies do not reflect the challenge to host cells by multi-species biofilms. Biofilm eradication is difficult, because they are highly resistant to antimicrobial agents and the host immune response (9, 10). Biofilms are involved in the pathogenesis of many inflammatory diseases, such as PD, as well as in urinary catheters and tracheal tube colonization (11-18).

*E. gingivalis* is one of seven *Entamoeba* species that infect humans, including *E. histolytica*, which causes amoebic dysentery and amoebic liver abscesses. Both parasites are detected in cytologic and histopathologic analysis. Distinguishing the two species is very important for therapeutic purposes: *E. gingivalis* infection is treated with doses of metronidazole, whereas *E. histolytica* is sensitive to antibiotics such as paromicyn which is used to eradicate cysts from the intestinal lumen (23). *E. gingivalis* may be detected in the mouth and pharynx; it is a commensal, and is characteristic in patients with partial or total edentulism, poor oral health, and in immunodepressed patients (positive HIV and AIDS patients). In one study, Sefer et al. found *E. gingivalis* in 135 patients with oral diseases and in particular affected by PD (24). Another recent study describes a prevalence of 28.3% of *E. gingivalis* infection among 551 college students in Tangshan, China; students with oral disease, poor oral hygiene, not chewing xylitol gum had a higher prevalence than the others.
(25). Lucht et al. detected *E. gingivalis* in saliva or dental plaque of 13 HIV-positive patients (26). Two other studies have reported different results regarding the prevalence of *E. gingivalis* in periodontal pockets, with data ranging from 6% to 69% (27, 28). In a Turkish study involving 46 patients with poor oral hygiene and gingival disease, testing for *E. gingivalis* and *Trichomonas tenax* in the oral cavity, *E. gingivalis* was detected in 7 patients (19.44%), and *T. tenax* in one (2.17%) (29). An Iranian study, designed to evaluate the prevalence of *E. gingivalis* and *T. tenax* parasites in the oral cavity of 50 patients with PD and in 50 healthy subjects, found six patients with *E. gingivalis* and three with *T. tenax*, while in the control group only one subject was infected with *E. gingivalis* (30).

New therapeutic approaches for periodontal disease

The oral microbiota is constituted by a large number of bacteria species that form a biofilm. The biofilm includes both saprophytes and potentially pathogenic species. It is well understood that most destructive types of periodontal diseases occur due to the presence of pathogenic microorganisms colonizing the subgingival area and the suppression or eradication of these microbes results in improvement in periodontal health. The oral cavity is suitable for invasion of many microorganisms. *E. gingivalis* is considered an oral commensal, but demonstrates a pathogenic potential associated with PD, in particular in immunocompromised individuals.

A causative link between *E. gingivalis* and PD has never been demonstrated; however *E. gingivalis* is infrequently found in people without PD (27, 28). In addition, there is evidence that *E. gingivalis* could favour the onset and progression of PD. The controversial results observed, in particular in patients negative for clinical symptoms and positive for *E. gingivalis*, could be explained by a better understanding of the interactions between this protozoa and immune response. However, we can assert that *E. gingivalis* and PD are correlated. This relationship can open new therapeutical approaches for treating PD, particularly in those cases refractory to therapy. In fact, PD treatment has the aim of reducing oral infection, and preventing progression of the disease. PD non-surgical therapy with scaling and root planing associated with a high level of domestic oral hygiene, can prevent the onset of the disease and allow for the correct maintenance of oral health. Good oral hygiene aims to control bacterial plaque, but when the patient’s attention to oral hygiene decreases, it is possible to experience a recurrence of the disease. In addition, PD has periods of remission and exacerbation. So a control of oral microbiota may be reached by the administration of anti-parasitic drugs. The study of correlation between PD and *E. gingivalis* could also improve the battle against peri-implantitis (31-33).

Dental implants have had a great success in the last decades for replacing missing teeth in partially or totally edentulous patients. Even if the main factor for the success of implant dentistry is the quality of bone of the receiving sites (34-37), the bacteria and protozoa of periodontal disease also cause peri-implantitis (38).

PD is one of the most prevalent diseases in the world, and *E. gingivalis* is common in humans, therefore an anti-parasitic treatment may represent a new frontier in periodontal treatment.

REFERENCES