Neutrophil homeostasis and inflammation: novel paradigms from studying periodontitis.
Hajishengallis G, Chavakis T, Hajishengallis E, Lambris JD.

Abstract
Once viewed as simply antibacterial effector cells packed with antimicrobials, neutrophils are now increasingly appreciated for their regulatory roles in immunity and inflammation. The homeostatic regulation of neutrophils is thus crucial for optimal operation of the immune system. An attractive model to understand mechanistically the role of neutrophils is periodontitis, an oral inflammatory disease that is particularly sensitive to neutrophil alterations in numbers or function. The recruitment and proper activation of neutrophils are largely dependent on leukocyte integrins and complement. This review discusses how these processes are affected by host genetic or microbial factors leading to the development of periodontitis. For instance, both hypo- and hyper-recruitment of neutrophils as a result of deficiencies in the expression of β2 integrins or their negative regulators, respectively, causes unwarranted IL-17-dependent inflammatory bone loss. Moreover, microbial hijacking of C5aR (CD88) signaling in neutrophils impairs their antimicrobial function while promoting destructive inflammatory responses. These studies not only support the concept that neutrophil homeostasis is key to periodontal health but also reveal promising, new therapeutic targets as discussed in the review.

PMID: 25548253

Porphyromonas gingivalis virulence factors involved in subversion of leukocytes and microbial dysbiosis.
Zenobia C, Hajishengallis G.

Abstract
The oral bacterium Porphyromonas gingivalis has special nutrient requirements due to its asaccharolytic nature subsisting on small peptides cleaved from host proteins. Using proteases and other virulence factors, P. gingivalis thrives as a component of a polymicrobial community in nutritionally favorable inflammatory environments. In this regard, P. gingivalis has a number of strategies that subvert the host immune response in ways that promote its colonization and facilitate the outgrowth of the surrounding microbial community. The focus of this review is to discuss at the molecular level how P. gingivalis subverts leukocytes to create a favorable environment for a select community of bacteria that, in turn, adversely affects the periodontal tissues.

PMID: 25654623
Porphyromonas gingivalis manipulates complement and TLR signaling to uncouple bacterial clearance from inflammation and promote dysbiosis.


Abstract
Certain low-abundance bacterial species, such as the periodontitis-associated oral bacterium Porphyromonas gingivalis, can subvert host immunity to remodel a normally symbiotic microbiota into a dysbiotic, disease-provoking state. However, such pathogens also exploit inflammation to thrive in dysbiotic conditions. How these bacteria evade immunity while maintaining inflammation is unclear. As previously reported, P. gingivalis remodels the oral microbiota into a dysbiotic state by exploiting complement. Now we show that in neutrophils P. gingivalis disarms a host-protective TLR2-MyD88 pathway via proteasomal degradation of MyD88, whereas it activates an alternate TLR2-Mal-PI3K pathway. This alternate TLR2-Mal-PI3K pathway blocks phagocytosis, provides "bystander" protection to otherwise susceptible bacteria, and promotes dysbiotic inflammation in vivo. This mechanism to disengage bacterial clearance from inflammation required an intimate crosstalk between TLR2 and the complement receptor C5αR and can contribute to the persistence of microbial communities that drive dysbiotic diseases.

PMID: 24922578

Genetic and intervention studies implicating complement C3 as a major target for the treatment of periodontitis.

Maekawa T, Abe T, Hajishengallis E, Hosur KB, DeAngelis RA, Ricklin D, Lambris JD Hajishengallis G

Abstract
Chronic periodontitis is induced by a dysbiotic microbiota and leads to inflammatory destruction of tooth-supporting connective tissue and bone. The third component of complement, C3, is a point of convergence of distinct complement activation mechanisms, but its involvement in periodontitis was not previously addressed. We investigated this question using two animal species models, namely, C3-deficient or wild-type mice and nonhuman primates (NHPs) locally treated with a potent C3 inhibitor (the compstatin analog Cp40) or an inactive peptide control. In mice, C3 was required for maximal periodontal inflammation and bone loss, and for the sustenance of the dysbiotic microbiota. The effect of C3 on the microbiota was therefore different from that reported for the C5α receptor, which is required for the initial induction of dysbiosis. C3-dependent bone loss was demonstrated in distinct models, including Porphyromonas gingivalis-induced periodontitis, ligature-induced periodontitis, and aging-associated periodontitis. Importantly, local treatment of NHPs with Cp40 inhibited ligature-induced periodontal inflammation and bone loss, which correlated with lower gingival crevicular fluid levels of proinflammatory mediators (e.g., IL-17 and RANKL) and decreased...
osteoclastogenesis in bone biopsy specimens, as compared with control treatment. To our knowledge, this is the first time, for any disease, that complement inhibition in NHPs was shown to inhibit inflammatory processes that lead to osteoclastogenesis and bone loss. These data strongly support the feasibility of C3-targeted intervention for the treatment of human periodontitis.

PMID: 24808362

Hirschfeld J

Abstract
BACKGROUND:
The majority of microbial infections in humans are biofilm-associated and difficult to treat, as biofilms are highly resistant to antimicrobial agents and protect themselves from external threats in various ways. Biofilms are tenaciously attached to surfaces and impede the ability of host defense molecules and cells to penetrate them. On the other hand, some biofilms are beneficial for the host and contain protective microorganisms. Microbes in biofilms express pathogen-associated molecular patterns and epitopes that can be recognized by innate immune cells and opsonins, leading to activation of neutrophils and other leukocytes. Neutrophils are part of the first line of defense and have multiple antimicrobial strategies allowing them to attack pathogenic biofilms.

OBJECTIVE/DESIGN:
In this paper, interaction modes of neutrophils with biofilms are reviewed. Antimicrobial strategies of neutrophils and the counteractions of the biofilm communities, with special attention to oral biofilms, are presented. Moreover, possible adverse effects of neutrophil activity and their biofilm-promoting side effects are discussed.

RESULTS/CONCLUSION:
Biofilms are partially, but not entirely, protected against neutrophil assault, which include the processes of phagocytosis, degranulation, and formation of neutrophil extracellular traps. However, virulence factors of microorganisms, microbial composition, and properties of the extracellular matrix determine whether a biofilm and subsequent microbial spread can be controlled by neutrophils and other host defense factors. Besides, neutrophils may inadvertently contribute to the physical and ecological stability of biofilms by promoting selection of more resistant strains. Moreover, neutrophil enzymes can degrade collagen and other proteins and, as a result, cause harm to the host tissues. These parameters could be crucial factors in the onset of periodontal inflammation and the subsequent tissue breakdown.

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Restoring host-microbe homeostasis via selective chemoattraction of Tregs.

Garlet GP, Sfeir CS, Little SR.

Abstract
The disruption of host-microbe homeostasis at the site of periodontal disease is considered a key factor for disease initiation and progress. While the downstream mechanisms responsible for the tissue damage per se are relatively well-known (involving various patterns of immune response operating toward periodontal tissue destruction), we are only beginning to understand the complexity of host-microbe interactions in the periodontal environment. Unfortunately, most of the research has been focused on the disruption of host-microbe homeostasis instead of focusing on the factors responsible for maintaining homeostasis. In this context, regulatory T-cells (Tregs) comprise a CD4+FOXp3 +T-cell subset with a unique ability to regulate other leukocyte functions to avoid excessive immune activation and its pathological consequences. Tregs act as critical determinants of host-microbe homeostasis, as well as determinants of a balanced host response after the disruption of host-microbe homeostasis by pathogens. In periodontitis, Tregs play a protective role, with their natural recruitment being responsible for conversion of active into inactive lesions. With controlled-release technology, it is now possible to achieve a selective chemoattraction of Tregs to periodontal tissues, attenuating experimental periodontitis evolution due to the local control of inflammatory immune response and the generation of a pro-reparative environment.

PMID: 25056995

Leukocyte production of inflammatory mediators is inhibited by the antioxidants phloretin, silymarin, hesperetin, and resveratrol.

Fordham JB, Naqvi AR, Nares S

Abstract
Antioxidants possess significant therapeutic potential for the treatment of inflammatory disorders. One such disorder is periodontitis characterised by an antimicrobial immune response, inflammation, and irreversible changes to the supporting structures of the teeth. Recognition of conserved pathogen-associated molecular patterns is a crucial component of innate immunity to Gram-negative bacteria such as Escherichia coli, as well as the periodontal pathogen Aggregatibacter actinomycetemcomitans. In this study, we investigated the antioxidants Phloretin, Silymarin, Hesperetin, and Resveratrol to ascertain whether they altered the production of inflammatory mediators by innately-activated leukocytes. Peripheral blood mononuclear cells were stimulated with lipopolysaccharide purified from Aggregatibacter actinomycetemcomitans, and the production of cytokines, chemokines, and differentiation factors was assayed by enzyme-linked immunosorbent assay, cytometric bead array, and RT-PCR. Significant inhibition of these factors was achieved upon treatment with Phloretin, Silymarin, Hesperetin, and Resveratrol. These data further characterise the potent anti-inflammatory properties of antioxidants. Their ability to inhibit the production of inflammatory cytokines, chemokines, and differentiation factors by a heterogeneous population of leukocytes has clear implications for their therapeutic potential in vivo.

PMID: 24707119