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Letter to Editor

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Modern Trends in Oral Biology Research

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To the Editor:

Within mainstream oral biology, research is predominantly focused on the study of dental caries and periodontal diseases which are primarily influenced by complex interactions among oral microbes and between oral microbes and the host, respectively. Moreover, the maintenance of a homeostatic balance between oral microbes and host responses is of utmost importance for the preservation of both oral and systemic health due to their intricate comorbidities. A recent article review by Hajishengallis *et al.*(1), and Hajishengallis G(2) meticulously explained these associations.

In the Cariology field, it has now become more evident that the complex interplay among the bacterial community as well as the inter-species interaction between fungi and bacteria have contributed significantly to the pathogenesis and severity of dental caries.(3,4) It was previously believed that diverse microbial species within the oral cavity randomly established their habitats. However, recent evidence has demonstrated that the disease-causing microbial community, in fact, exhibits a unique and organized spatial structure where Streptococcus mutans aggregate as an inner core and are surrounded by other bacterial or fungal species. These corona-like arrangements not only aid in disease-causing processes for microbial communities but also protect from potentially harsh environments.(1)

S. mutans is a keystone cariogenic bacterium that has been clinically associated with dental caries. Other bacterial species including *Streptococcus gordonii* and *Streptococcus oralis* have also been shown to contribute to disease progress and severity. However, a more recent report(4) analyzed comprehensive taxonomic association in metagenomics and metatranscriptomics data obtained from the supragingival plaque of 300 children, and discovered several new bacterial species with strong association with dental caries. The leading species were *Selenomonas sputigena, Prevotella salivae,* and *Leptotrichia wadei.* Among these bacteria, *S. sputigena* is a flagellated anaerobic bacterium found in subgingival microbiota and has no prior reports on the involvement in dental caries biofilm. This study demonstrated, for the first time, the unrecognized role of *S. sputigena* in dental caries pathogenesis which involves an interaction with S. mutans as a pathobiont that enhances biofilm virulence, thus exacerbating dental caries severity *in vivo.*(4)

The research into dental caries management and prevention has progressively advanced to date. The studies cover a range of topics from enhancing the efficacy of existing methods to developing entirely new strategies. Fluoride application has been widely acknowledged as an effective prevention for dental caries. For example, stannous fluoride (SnF_2) is a commonly used anticaries agent due to its antibacterial and antibiofilm activities. However, one major limitation of SnF_2 is that it is susceptible to degradation in aqueous solution requiring chemical additives which, in turn, reduce the fluoride bioavailability. Ferumoxytol is a Food and Drug Administration (FDA)-approved iron oxide nanoparticle solution used for the treat-

ment of iron deficiency. Interestingly, Ferumoxytol has recently been shown to effectively eradicate cariogenic biofilm from tooth surfaces *in vitro* and *in vivo*. While Ferumoxytol is a very promising antibiofilm agent, it does not prevent or revert the demineralization process on tooth enamel. Surprisingly, a recent finding by Huang *et al.*[5] discovered a notable synergistic effect of SnF_2 and Ferumoxytol where a progression of dental caries is completely immobilized following the use of SnF_2 and Ferumoxytol combination. The authors revealed that the combination helps stabilize the SnF_2 as well as enhance enamel resistance against the demineralization process without affecting oral microbiota or other surrounding tissues.[5] Nevertheless, the removal of biofilm in extremely small or hard-to-reach areas remains challenging due to their inaccessibility. Microrobotics which operates at scales from micrometers to millimeters has recently been designed for biofilm removal in such areas. Microrobotics is a highly advanced and efficient technology that enables precise control and navigation of microrobots to the biofilm-infected site. These microrobots are equipped with magnetic nanoparticles called ferrofluids, which can be manipulated to provide physical disruption of the biofilm.[6,7] Furthermore, microrobotics also allows for the delivery of catalytic nanoparticles known as nanozymes, which can further enhance antimicrobial activity chemically.[7,8] This groundbreaking technology has the potential to improve the standard of care for biofilm-related infections.

Periodontology, on the other hand, is driven by the collective interconnections between polymicrobial dysbiosis and exaggerated host inflammatory responses. Whether the dysbiotic microbiome caused periodontal inflammation or if the breakdown of periodontal tissues favored pathogenic microbes leading to dysbiosis, is controversial. However, findings by Payne *et al.*[9] demonstrated using mouse models of vertical and horizontal transmissions of dysbiotic microbiome that a dysbiotic microbiome precedes periodontal disease. Further corroborating this notion, a recent report showed that bacteria exploiting the altered environment to flourish do not necessarily exacerbate the disease. According to Chipashvili *et al.*,[10] the epibiont species Saccharibacteria, which is commonly found in the microbiome of periodontitis patients, thrives in an inflammatory environment. However, this bacterium offers protection to the mammalian host by reducing the pathogenicity of other bacteria in the vicinity, thereby reducing inflammatory alveolar bone loss.

While the current therapeutic strategy for periodontitis emphasizes the physical and chemical removal of bacterial plaque, numerous reports on immunomodulation are emerging. Complement activation has long been implicated in periodontitis and it is believed that targeting complement activation could ameliorate periodontal disease severity.[11,12] Remarkably, a myriad of complement-targeting inhibitors has been investigated in clinical trials. Among these, a C3-targeting compound known as AMY-101 was investigated in a phase II clinical trial and showed sustainable resolution of gingival inflammation in patients with periodontal inflammation.[13] This study suggests that using immunomodulation as an adjunct to traditional periodontal treatment is a promising strategy.

Oral biology research has made notable strides in recent years. In addition to cariology and periodontology, various other oral biology disciplines have also made substantial progress in the field. These advancements can broaden our perspectives not only in terms of research methodology, but also in how discoveries are made. Nonetheless, the ultimate goal remains to enhance our understanding of oral health and diseases, which can pave the way for improved prevention, diagnosis, and treatment strategies.

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