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Martha J Somerman,
Frontiers in Dental Medicine, United States

*CORRESPONDENCE
Nadya Lumelsky
nadya.lumelsky58@gmail.com

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Oral-systemic immune axis: Crosstalk controlling health and disease

Nadya Lumelsky*

National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH), Bethesda, MD United States

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Introduction

The overall mission of Frontiers in Dental Medicine is to advance interdisciplinary research addressing how oral health and disease can be understood within the context of the whole body. The Journal strives to integrate oral and systemic health for the benefit of overall health. Within this mission, the Oral Systemic Immunology Section is focused on the immune system seen as an integrator of oral and systemic health. We believe that identifying, dissecting, and learning to control the immune mechanisms linking oral and systemic diseases will lead to advances in clinical medicine as well as public health. Chronic oral inflammatory conditions, such as periodontal disease, are highly prevalent in the US population, with approximately 2 in 5 adults being affected with some form of periodontal disease. Unfortunately, this serious condition is often neglected until its late stages. Other chronic oral inflammatory diseases, such as caries and peri-implantitis (1), among others, have also been linked to systemic diseases and too often remain untreated. Additional effort is needed to understand the mechanisms of oral and systemic inflammatory disease interaction; these advances will not only result in improvement of oral health but will also provide therapeutic strategies for addressing treatment of a multitude of systemic diseases.

Oral-systemic connection: correlative or causal?

Immunology of the oral cavity has been a focus of active research for many years and significant advances have been made in the mechanistic understanding as to how the immune system controls oral homeostasis. Also, over the years there have been numerous reports of oral inflammatory diseases exerting negative effects on other systems in the body, such as cardiovascular and nervous systems. Further, oral inflammatory diseases were found to increase a severity of obesity, kidney diseases, and Type 2 diabetes (2–6). These associations are bi-directional, as systemic inflammatory conditions often exacerbate oral diseases (7, 8). While compelling, the evidence of an oral-systemic connection has often been circumstantial and correlative rather than causal. Recent results pointing to a unifying role of innate and adaptive immunity in health and disease across different organs suggest that different

inflammatory comorbidities might be functionally linked with each other; these findings created a motivation for re-examining the oral-systemic disease connection at a mechanistic level (9–11).

For example, it has recently been suggested that a known association between periodontal disease and arthritis may be explained by a phenomenon called maladaptive trained innate immunity (12). Trained immunity arises from inflammatory or microbial challenges early in life resulting in a heightened responsiveness that enables the host to respond stronger to future challenges later in life. Such adaptation, which is thought to be enabled by the epigenetic "immune memory" of hematopoietic stem and progenitor cells in the bone marrow, has beneficial protective functions allowing a fast mobilization of the immune system against a variety of infections and tumors. However, under chronic inflammatory conditions, protective trained immunity often evolves into maladaptive trained immunity and becomes detrimental to health. It has been suggested that maladaptive bone marrow-mediated response might underlie a causal link between inflammatory diseases of the oral cavity and systemic inflammatory diseases. In agreement with this hypothesis, periodontitis-induced maladaptive trained immunity was found to be transmissible by bone marrow transplantation to naive recipients in a mouse model; these mice exhibited increased inflammatory phenotype and increased susceptibility to inflammatory arthritis (12).

For atherosclerosis-periodontal disease connection, it has been proposed that bacterial by-products released from the inflamed periodontal pocket may stimulate cytokine production by the resident inflammatory cells, and that these cytokines might exacerbate atherosclerotic inflammation (13). The work's authors have also implicated bone marrow as a potential key participant in this process and provided human imaging data to corroborate the potential causal relationship between periodontal disease and atherosclerosis. Interestingly, lipoxins and resolvins, which belong to a class of endogenous pro-resolving mediators (14), were shown to alleviate both periodontitis and vascular inflammation in animal models (15), suggesting that boosting systemic inflammation resolution may represent a viable therapeutic approach for simultaneous targeting of multiple inflammatory comorbidities.

Adaptive immunity has also been implicated in the oral-systemic disease axis. For example, *Porphyromonas gingivalis* (*P. gingivalis*), a gram-negative oral anaerobic bacterium that plays a key role in the pathogenesis of periodontal disease, is known to suppress adaptive immunity allowing *P. gingivalis* to exist in the host tissues and resulting in chronic inflammatory responses. It has been suggested that *P. gingivalis* not only exerts immune suppressive effects on B and T cells in the periodontium but has similar effects in the vascular system in atherosclerosis and in the brain in Alzheimer's disease. In periodontitis this bacterium inhibits the synthesis of interleukin-2 and increases humoral responses while activating several downstream inflammatory signaling cascades (16, 17).

Challenges and opportunities

A body of evidence linking oral and systemic diseases is growing. However, additional effort is needed to improve our mechanistic understanding of the bidirectional interactions between oral and systemic environments under normal and pathological conditions, to definitively demonstrate a causal link between oral and systemic diseases, to develop effective *in vitro* and *in vivo* tools and strategies to address these mechanistic questions, and to capitalize on this knowledge for treatment of oral and systemic comorbidities. To address these challenges, this Oral Systemic Immunology Section invites basic, translational, and clinical science contributions focused on all aspects of immunological interactions between the oral cavity and the rest of the body - including, but are not limited to, the following:

Oral microbiome and systemic health and disease

The oral microbiome is the second most varied microbiome in the body after the gut. It contains about seven hundred different species of bacteria and hosts numerous fungi, viruses, and protozoa species. These microorganisms shape and guide the function of the oral mucosal immunity, and link mucosal immunity to many diseases of the oral cavity (18). Also, numerous studies implicated the oral microbiome in systemic inflammatory diseases, including cardiovascular and neurodegenerative diseases, obesity, and several types of cancer, among others.

How oral microorganisms influence distant sites in the body, and how the immune system-mediated signaling regulate these trans-tissue/organ interactions is still poorly understood (19, 20). Systemic expansion of pathogenic oral microbiota, inflammatory cell transmigration from the oral cavity, and oral microbiome-innate and -adaptive immune system crosstalk have all been implicated as possible links between oral microbial environment and systemic diseases. It is also reasonable to expect that in certain cases the oral microbiome and mucosal immunity serve a protective function and mediate systemic resolution of inflammation at distal sites. For example, nutrition-mediated influences on the composition of oral microbiome may serve as positive and negative regulators of systemic homeostasis, as has been reported for the gut microbiome (21).

Cellular and molecular mediators of oral systemic immune crosstalk

While extensive research effort has been devoted to this area, recent advances in single cell omics analyses (transcriptomics, epigenomics, metabolomics, proteomics), system biology, bioinformatics, machine learning, and artificial intelligence have created new opportunities for exploring signaling networks that control immune interactions between the oral environment and the rest of the body at an unprecedented level of resolution and precision (22–24). As discussed above, bone marrow stem and progenitor cells and myeloid cells are becoming increasingly implicated in the establishment of a maladaptive trained immunity, suggesting that the bone marrow may provide a functional link between oral and systemic diseases *via* common inflammatory signals originating from the bone marrow (10, 12). It will be important to apply single cell analysis and system biology approaches to further define the cellular repertoire and signaling networks controlling progression from acute to chronic inflammation and to maladaptive trained immunity in the relevant preclinical animal models. It is also of interest to elucidate how cytokines, chemokines, pro-resolving mediators and their signaling pathways contribute to the network of intercellular interactions responsible for oral-systemic immune homeostasis in health and disease.

Unique and shared biomarkers of oral and systemic diseases

Prevention, diagnosis, and treatment of linked oral and systemic diseases will be critically dependent on the availability of appropriate biomarkers for evaluating risks of transition from oral to systemic disease states. Such biomarkers will also be needed for monitoring therapeutic interventions. One example of such a potential biomarker is the presence of lipopolysaccharide (LPS) in the circulation. LPS is a virulence factor of gram-negative bacteria, which can originate from gut or periodontal lesions; it activates both the innate and adaptive immunity. Translocation of LPS into systemic circulation leads to endotoxemia. Healthy subjects have low circulating LPS activity, but chronic endotoxemia was shown to be involved in the pathogenesis of many inflammation-driven systemic diseases, including atherosclerosis, obesity, liver diseases, diabetes, and metabolic syndrome, where the presence of LPS in the circulation is considered a risk factor and a predictive biomarker for developing of cardiometabolic diseases (25).

Also, it had been reported that in periodontal disease-related oral dysbiosis the presence of oral pathogens-specific antibodies in the circulation may mark an increased risk for a subclinical atherosclerosis and might predict future coronary artery disease or stroke (26). Interestingly, the risk for developing oral dysbiosis appears to correlate with a level of potassium in the periodontal pocket. High potassium level was associated with an increased virulence of the oral microbiota, which in turn altered the inflammatory status of a gingival epithelium toward elevated production of several inflammatory cytokines (27). As the list of biomarkers linking oral and systemic diseases grows, it will be important not only to verify their association with specific diseases, but to definitively establish the biomarkers' predictive power in preclinical animal models and in clinical settings.

In vitro and *in vivo* experimental tools and models

One of the key obstacles that limit establishing causal relationships between oral and systemic diseases is the paucity of appropriate experimental small and large animal models for such definitive experiments. To derive effective animal models, it is important to establish chronic inflammatory conditions that mimic these conditions in humans, such as those characterizing human periodontitis, peri-implantitis and other oral diseases (28–30). Mouse is an attractive model, because of the availability of multiple genetic variants and the ease of genetic manipulation. However, large animal models, such as pig inflammatory disease models, are urgently needed, since pig's anatomy, physiology, immune system, disease pathology, and longer life span more closely mimic human parameters than those of rodents. Advanced tools, including imaging tools, are also needed to conduct the analyses in live animals longitudinally where the level of inflammation can be directly measured and progression from single to multi-organ disease monitored (31, 32).

In vitro reductionist systems generally do not possess sufficient complexity to mimic multi-tissue and multi-organ interactions *in vivo*. However, recent advances in 3-dimentional microfluidic systems - tissue and organ chips - hold significant promise (33, 34). Some such systems are designed to functionally integrate into a single platform, chips representing different tissues or organs, including the immune system; such multi-component platforms are sometimes referred to as "body-on-a-chip" (35, 36). An additional advantage of chip systems is that they are based on human rather than animal cells and thus provide readouts reflective of unique human physiology. Tissue and organ chips have been widely used for many applications, including drug/toxicity screening and disease modeling, and they offer exciting opportunities for investigation of oral-systemic disease connections.

Conclusions

Re-examining oral-systemic disease connection on a mechanistic level is particularly timely now in view of recent advances in the understanding as to how innate and adaptive immune systems integrate inflammatory signals throughout the body. Further, unprecedented opportunities for this work have been created by recent technological breakthroughs in single cell analyses, system biology, and other computational sciences, as well as by *in vitro* and *in vivo* experimental models recapitulating human disease-relevant inflammatory pathways. The field is ready to transition from the observational correlative studies of the past to studies directly addressing causal relationships between oral and systemic diseases. Meeting these goals will require a highly interdisciplinary effort and collaboration of dentists, physicians, biologists, immunologists, bioengineers, and computational scientists. We hope that the Oral Systemic Immunology Section will help to move the field forward by promoting and publishing the best quality science, to benefit the scientific community and to bring effective therapies to the clinic.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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