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Editorial

Oral-Systemic Health and Disorders: Latest Advances on Oral–Gut–Lung Microbiome Axis

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The human body hosts complex microbial communities, accounting for 100 trillion microbial symbionts, much more than human cells, aiding nutrition, counteracting pathogens, and collaborating with our immune system [1]. Host-associated microorganisms, comprising the bacterial microbiome, the mycobiome, and the virome, are acquired after birth through vertical transmission and later shaped throughout life by environmental exposure. While the gut consists of 90% of all human microbiota, the oral cavity harbors the second most abundant microbial symbionts after the gastrointestinal tract [1]. Microbiome disruption, defined as dysbiosis, is etio-pathogenically linked to several disorders involving a multitude of organs and systems. In this perspective, the gut and the oral cavity, being the two largest microbial habitats, play a significant role in microbiome-associated diseases, as well as through the proposed inter-connections with pulmonary, hepatic, mucosal, and cutaneous microbiomes [2–6].

In particular, the bi-directional communication network, also known as the gut lung axis connecting the intestinal and pulmonary microbiota, is considered responsible for the massively increased bacterial load in the cecum after acute lung injury, causing alterations in airway microbiota and its transitory translocation into the bloodstream toward the bowel [7,8]. Moreover, subjects with chronic obstructive pulmonary disease often show intestinal hyper-permeability and a high prevalence of IBD [9]. Furthermore, respiratory viral infections, which are frequently accompanied by gastrointestinal symptoms or gut dysfunction [8], have been proven to alter the gut microbiome, which indirectly regulates macrophage response to the respiratory pathogens and is, therefore, essential for activating the innate immune responses against pulmonary infections [10]. Indeed, as a counterpart, it has also been demonstrated that immune cells from the gut gain access to the systemic circulation and reach the respiratory tract, encouraging the host's ability to fight infections. Through a similar mechanism, in subjects suffering from inflammatory bowel disease, intestinal pro-inflammatory cytokines may, through the bloodstream, alter pulmonary inflammatory mediator levels, thus affecting the local micro-environment in the lung and reducing lung function [7]. Accordingly, increased Clostridia and reduced Bifidobacteria species in the gut have been related to asthma in childhood [11], and it has been proposed that by sustaining the balance of gut microecology, probiotic administration may also prevent secondary respiratory bacterial infections [8]. Therefore, the gut–lung axis may coordinate both physiologic and pathologic immune responses, being reciprocally implied in infectious and inflammatory diseases and disorders of both the lung and gut [8].

Both the respiratory and the gastrointestinal tracts are directly connected to the oral cavity, although the oral and gut microbiome profiles remain segregated by the oral–gut barrier in physiological conditions [12]. However, intestinal microbiota may reach the oral cavity through inter- and intra-personal transmission, and the oral microbiota can translocate to the gut due to oral–gut barrier dysfunction [12]. Like gut microbiota, which is crucially implied in immunity and metabolism, the oral microbiome modulates oral, dental, and periodontal pathophysiology in both a pathogen-dependent and collective manner and affects systemic health conditions [6,12]. Indeed, oral dysbiosis is putatively associated

Citation: Amato, A. Oral-Systemic Health and Disorders: Latest Advances on Oral–Gut–Lung Microbiome Axis. *Appl. Sci.* **2022**, *12*, 8213. https://doi.org/10.3390/app12168213

Received: 7 August 2022
Accepted: 16 August 2022
Published: 17 August 2022

with systemic diseases [13,14]. In the case of periodontitis, an oral dysbiotic disease [15–18], suspected periodontopathogens could induce, locally and systemically, a chronic inflammatory state, stimulating the immune response and inflammatory transcription factors, including Nuclear Factor K-beta [19–21]. In fact, immune-inflammatory dysregulation is considered the primary key mechanism underlying the potential association of periodontitis with multiple systemic disorders [19–21]. Secondarily, virulence factors specific to oral bacteria, especially Fusobacteria species, may also be involved, translocating to distant organs or releasing toxins into the bloodstream [19–22]. Both mechanisms would underlie the association between periodontitis and inflammatory and degenerative diseases, such as atherosclerosis, Alzheimer's disease, age-related macular degeneration [22], chronic inflammatory bowel disease [23], and solid neoplasms, such as colorectal carcinoma [24].

Moreover, intestinal microbes could, due to mucosal barrier impairment, translocate to the liver through the biliary tract and the portal vein, and oral dysbiosis could exacerbate chronic liver diseases, likely modulating the gut ecosystem through the oral–gut axis, on the one side, and may reflect the intestinal dysbiotic ecosystem, affected in turn by hepatic diseases, on the other side [12,25].

Furthermore, mainly the upper but also the lower airways of healthy individuals frequently harbor oral anaerobes, including Prevotella and Veillonella species, probably secondary to continuing microaspiration by contiguity. Thus, detecting oral bacterial DNA in the lower airways in healthy subjects could represent the traces of aspirated oral bacteria either not eliminated through physiological clearance or living in dynamic equilibrium with host defensive responses by promoting mucosal immunity of the Th17/neutrophilic phenotype and suppressing innate immunity. Whether bacteria from the oral microbiome regulate responses to pulmonary pathogens and whether they interfere in inflammatory lung disease pathogenesis [26] is still under study.

Therefore, a growing body of evidence highlights that gut and oral dysbioses, interconnected with the local microbial and inflammatory environment of the lung, liver, and other organs, are crucially implied in a multitude of diseases also involving distant organs. It may be proposed that the bidirectional crosstalk between the oral, gut, and lung microbiomes, based on direct microbial translocation and indirect secretomes effects, may develop the oral–gut–lung axis [24], which may in turn play a crucial pathogenic role in several diseases.

However, to date, most of the investigations on microbiome-associated diseases still focus on a single organ-specific, rather than inter-organ, microbiome, and the potential role of the oral–gut–lung axis in the onset and progression of various human infectious, degenerative, inflammatory, and neoplastic disorders through local and systemic dysbiotic phenomena and immune-inflammatory dysregulation remains to be elucidated. Further studies are needed to highlight the potential role of probiotics, oral hygiene and antisepsis, and periodontal treatment in managing oral, dental, and periodontal dysbiosis [27] and the related interconnections with the microbiome from respiratory and gastrointestinal tracts.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

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