Oral-gut connection: one step closer to an integrated view of the gastrointestinal tract?

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Although an enrichment of orally derived bacteria is reported in the gut microbiota of patients with several diseases, it is mostly unknown whether oral bacteria can colonize and induce intestinal inflammation. In a recent paper in Science, Atarashi *et al.*[1] from Kenya Honda's laboratory show that a subset of orally derived bacteria colonizes and persists in the gut, leading to activation of the intestinal immune system and subsequent chronic inflammation in a susceptible host. The impact of oral health status as a potential contributor to inflammatory diseases at distal sites of the body deserves consideration.

INTRODUCTION

The oral cavity is a complex environment encompassing distinct, smaller microbial habitats, such as teeth, buccal mucosa, soft and hard palate, and tongue, which form a species-rich heterogeneous ecological system. Pathological processes of the oral cavity, such as caries and periodontal diseases, are known to result from the disturbed equilibrium between the microbiota and the host. However, more recently it has been noted that disturbances of the oral microbiota might also be linked to systemic diseases. On one hand, the oral microbiota is altered in patients with systemic diseases, such as rheumatoid arthritis and inflammatory bowel disease (IBD).[2,3] On the other hand, orally derived microorganisms have been reported to be enriched in the gut microbiota of patients with several diseases.[4,5] These results suggest an interplay between oral and gut ecosystems, where oral bacteria might colonize the gut and contribute to the emergence of chronic inflammatory diseases.

In a recent *Science* paper Atarashi *et al.*[1] found that a subset of orally derived bacteria ectopically colonizes and persists in the gut and contributes to activation of the intestinal immune system, leading to chronic inflammation. Saliva samples from two patients with Crohn's disease (CD) were injected into C57BL/6 germ-free (GF) mice by gavage. One transplanted saliva sample resulted in a marked increase of T helper 1 (Th1) IFN-γ^+CD4$^+$ cells in the intestinal lamina propria. The authors identified *Klebsiella pneumoniae* 2H7 (Kp-2H7), which mainly colonized colon and cecum, as the major contributor to the accumulation of Th1 cells. In specific pathogen-free mice, antibiotic exposure disrupted the colonization resistance provided by members of the gut microbiota allowing Kp-2H7 to colonize the gut and induce colonic Th1 cells. Interestingly, Kp-2H7 colonization did not induce inflammatory changes in wild-type mice, either GF or ampicillin-treated specific pathogen-free, but did so in Il10$^{-/-}$ mice. These findings indicate the *Klebsiella* strain colonizes the gut in the context of dysbiotic intestinal microbiota and can act as a pathobiont in a genetically susceptible host. The investigators also revealed Toll-like receptor signaling and dendritic cells contributed to *Klebsiella*-induced Th1 accumulation. Moreover, interferon (IFN)-γ and IFN-inducible genes in epithelial cells and dendritic cells contributed to sustained accumulation of Th1 cells. Another *Klebsiella* strain, *K. aeromobilis* 11E12, isolated from a saliva sample of a patient with active ulcerative colitis, also induced a strong Th1 response in the intestine. *K. pneumoniae* Kp-40B3, from a saliva sample of a healthy donor, could also induce Th1 accumulation in the colon of monocolonized mice. After mining their 16S rRNA gene-sequencing data, Atarashi *et al.*[1] found that the aggregated relative abundance of *Klebsiella* species was significantly increased in patients with CD, primary sclerosing cholangitis, and alcoholism in comparison to healthy controls, and genes correlated with *Klebsiella*-mediated Th1 response were enriched in the fecal microbiota of IBD patients carrying *Klebsiella* species.

The invasion of the gut by oral bacteria is not a new concept. The mouth is the major gateway for the body. Food enters

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the mouth and together with saliva passes on to the stomach and intestine, and air passes through the mouth on the way to the lungs. Therefore, it is likely microorganisms from the oral cavity might spread and colonize other areas.[6] Studies have identified orally derived species, most commonly from the *Prevotella*, *Veillonella*, or *Streptococcus* taxa, in the intestinal microbiota in different contexts. In treatment-naive CD patients, oral species are found to be increased in the gut microbiota.[4] Also, over 50% of the species enriched in the gut microbiota of patients with liver cirrhosis are of buccal origin.[5] *Fusobacterium nucleatum*, an oral commensal that is involved in periodontal disease, is found at higher abundance in stool from patients with colorectal carcinoma and adenoma, and it accelerates colonic tumorigenesis in $Apc^{Min/+}$ mice through modulation of the host immune function.[7] Further, alterations in the ileal microbiota are found in mice swallowing *Porphyromonas gingivalis*, a periodontopathogen.[8] However, evidence has so far been scarce about the capacity of oral bacteria to colonize and mediate inflammatory responses in the intestine. The findings by Atarashi *et al.*[1] have now revealed that pathobionts residing in the oral cavity can colonize and induce inflammation in the gut.

One remarkable contribution to the field would be to identify the oral health status of the included individuals in the study by Atarashi *et al.*[1] In fact, this has frequently been overlooked in studies assessing the relationship between oral microbiota and systemic diseases. The salivary microbiota is heterogeneous even within a healthy oral ecosystem, where different community types related to salivary biochemical host parameters seem to exist.[9] Moreover, there is robust evidence that altered microbial profiles and disturbed host–microbe interactions are central to common oral diseases, such as dental caries and periodontal diseases (**Box 1**). In caries compared to healthy, oral microbiota present on the tooth surface increases in complexity at the initiation of the lesion and then shows decreased diversity in the established lesion, probably due to an acidic environment.[10] This is also reflected in the salivary microbiota, where reduced diversity and increased prevalence of acidogenic and aciduric streptococci are seen in patients with caries.[11] In periodontitis, oral microbiota shows greater complexity with higher proportions of pathobionts and keystone pathogens, such as *P. gingivalis*.[10] Similarly, an altered microbial profile with higher levels of putative periodontal pathogens, such as *Parvimonas micra* and *Filifactor alocis*, is detected in saliva from periodontitis patients.[12] Thus, it would be particularly interesting to find out whether a certain salivary microbial community is associated with *Klebsiella* strains and whether oral diseases facilitate the colonization by these strains. Out of the six saliva samples included in the study by Atarashi *et al.*,[1] three yielded *Klebsiella* strains with Th1-inducing capacity. Whether this was associated with the oral health status warrants investigation. Early reports suggested that alterations in the salivary flow and pH could predispose to intraoral colonization with *K. pneumoniae*, and the periodontal pocket (a space that forms in the gingival sulcus between teeth and gums in periodontitis) could act as a reservoir for enterobacterial species, such as *K. pneumoniae*,[13,14] possibly increasing the risk of gut colonization by pathobionts. Therefore, oral dysbiosis might be associated with gut dysbiosis, and contribute to inflammatory diseases or perpetuation of disease at distal sites of the body. However, to gain insight into this interplay, oral health status should be taken into consideration. Although investigations are needed, strategies designed to prevent or modulate the colonization of the oral cavity by pathobionts, especially *Klebsiella* strains, might have a positive impact on intestinal inflammation.

Box 1. Definitions of common oral diseases.

Dental caries: a multifactorial disease that results in the destruction of the dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates, and might lead to dental pain and tooth loss. It results from an imbalance in the physiological equilibrium between the oral microbiota and tooth minerals (reviewed in Selwitz *et al.*[15]).

Periodontal disease: a biofilm-induced chronic inflammatory condition that affects the tooth-supporting structures (gingiva, periodontal ligament, and bone). Gingivitis, the initial lesion, is a reversible inflammation of the soft tissue (gingiva). Periodontitis, the advanced lesion, results in progressive loss of attachment and bone, which in its severe form can lead to tooth loss and contribute to systemic inflammation (reviewed in Kinane *et al.*[16]).

DISCLOSURE

The authors declared no conflict of interest.

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