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The Bacterial Connection between the Oral Cavity and the Gut Diseases

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Abstract

More than 100 trillion symbiotic microorganisms constitutively colonize throughout the human body, including the oral cavity, the skin, and the gastrointestinal tract. The oral cavity harbors one of the most diverse and abundant microbial communities within the human body, second to the community that resides in the gastrointestinal tract, and is composed of >770 bacterial species. Advances in sequencing technologies help define the precise microbial landscape in our bodies. Environmental and functional differences render the composition of resident microbiota largely distinct between the mouth and the gut and lead to the development of unique microbial ecosystems in the 2 mucosal sites. However, it is apparent that there may be a microbial connection between these 2 mucosal sites in the context of disease pathogenesis. Accumulating evidence indicates that resident oral bacteria can translocate to the gastrointestinal tract through hematogenous and enteral routes. The dissemination of oral microbes to the gut may exacerbate various gastrointestinal diseases, including irritable bowel syndrome, inflammatory bowel disease, and colorectal cancer. However, the precise role that oral microbes play in the extraoral organs, including the gut, remains elusive. Here, we review the recent findings on the dissemination of oral bacteria to the gastrointestinal tract and their possible contribution to the pathogenesis of gastrointestinal diseases. Although little is known about the mechanisms of ectopic colonization of the gut by oral bacteria, we also discuss the potential factors that allow the oral bacteria to colonize the gut.

Keywords: periodontal disease/periodontitis, bacteria, systemic health/disease, host-pathogen interactions, microbiology, mucosal immunity

Introduction

The human body is colonized by >100 trillion symbiotic microorganisms, almost equivalent to the number of human cells and collectively referred to as the human microbiota (Qin et al. 2010; Sender et al. 2016). Due to environmental differences, each site in the body is home to a distinct microbial ecosystem (Sender et al. 2016). Among these sites, the most diverse bacterial populations are found in the intestinal tract (Human Microbiome Project 2012; Blum 2017). The human gut microbiota contributes to host physiologic development and maintenance, including education of the host immune system, nutrient digestion, and defense against colonization by pathogenic microorganisms (Kamada, Seo, et al. 2013; Gilbert et al. 2018). Because of its enormous impact, disturbance of the gut microbiota, so-called gut dysbiosis, has been shown to underlie multiple intestinal pathologies, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and colorectal cancer (CRC). However, we lack a comprehensive understanding of which bacteria act as disease-associated pathobionts and how they contribute to the pathogenesis of disease. In this regard, it has been reported that patients with diseases of the gut exhibit an abnormal enrichment of typical oral bacteria in the luminal contents and the gut mucosal tissues (Gevers et al. 2014; Yachida et al. 2019). Thus, it is conceivable that the oral cavity serves as a reservoir of oral pathobionts whose ectopic gut colonization contributes to the pathogenesis of intestinal diseases.

The oral cavity is a primary gateway to the human body and has the second-largest and diverse microbiota after the gut, harboring >770 species of bacteria (Escapa et al. 2018). A variety of microbial habitats in the oral cavity (e.g., teeth, buccal mucosa, soft and hard palate, and tongue) makes the ecologic system complex and attracts diverse microorganisms, called oral microbiome, including bacteria, fungi, and viruses (Kilian 2018). Within oral microbiome, bacteria are the major components and form distinct microbial communities in each oral habitat; they primarily comprise members of the phyla *Firmicutes, Fusobacteria, Proteobacteria,* and *Actinobacteria* (Costalonga and Herzberg 2014). Diverse structural and

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nutritional difference creates a unique microbial ecosystem in each body site, benefiting human health. However, compelling evidence indicates that certain bacteria can be disseminated from one site to the others and cause systemic diseases. In this regard, numerous studies have elaborated that oral microbes can spread through the body and have been found in a variety of systemic diseases, such as cardiovascular diseases, adverse pregnancy outcomes, and rheumatoid arthritis (Hajishengallis 2015; Graves et al. 2019). Importantly, in addition to these sterile organs, oral microbes can be ingested and naturally translocate to the upper and lower digestive tract (i.e., esophagus, stomach, small and large intestine). Unlike sterile organs, the digestive tract harbors indigenous microbial communities that prevent the colonization of exogenous microbes that invade from the extraintestinal compartment (i.e., the mouth) via multiple means (Kamada, Chen, et al. 2013). However, under certain circumstances, oral microbes can ectopically colonize the upper and lower digestive tract. In this regard, increasing evidence suggests that ectopic colonization by oral microbes may be detrimental and cause diseases in the digestive tract. In this review, we summarize the current knowledge of the dissemination and its role of oral microorganisms in extraoral diseases, particularly diseases in the lower digestive tract. Among the oral microbiota, bacteria are the most well-studied microorganisms with respect to the possible involvement in extraoral diseases. Hence, in this review, we focus on the role that oral bacteria play in the pathogenesis of gastrointestinal diseases.

Oral Bacteria in Gut Pathology

Despite the environmental segregation of the mouth and gut, it has been reported that more than half of microbial species (e.g., *Streptococcus* and *Veillonella*) frequently detected in both sites show evidence of oral-gut translocation, even in healthy individuals (Schmidt et al. 2019). Gut colonization by oral bacteria such as *Veillonella* spp. is known to modulate host immunity (Geva-Zatorsky et al. 2017). Thus, ectopic colonization by oral bacteria in the healthy gut may in part contribute to the physiologic development and/or maintenance of gut immunity. However, ectopic gut colonization by specific oral bacteria and/or under certain conditions might be linked to the pathogenesis of diseases in the gastrointestinal tract. In Table 1, we define oral bacteria per the following criteria: 1) bacteria identified as a constituent of the oral microbiome by the Human Oral Microbiome Database (http://www.homd.org/) and 2) bacteria that have higher abundance in the oral cavity than in the gut samples of healthy individuals on the basis of the NIH Human Microbiome Project (HMP1; https://hmpdacc.org/hmp/). In addition, some bacteria that were previously reported as bacteria involved in oral pathology (e.g., some species/genera belonging to the Enterobacteriaceae family, *Staphylococcus, Fusobacterium varium*, and *Porphyromonas gingivalis*) are listed as possible oral bacteria even if they do not meet criterion 2 (see Appendix Table 1).

Irritable Bowel Syndrome

IBS is the most common functional gastrointestinal disorder, characterized by recurrent episodes of abdominal pain (Simren and Tack 2018). The global prevalence of IBS is estimated to be 11.2%, with geographic variations ranging from 7% to 21% (Lovell and Ford 2012; Canavan et al. 2014). A study revealed the approximately 7-fold increased risk of IBS development after microorganism-driven gastroenteritis (Halvorson et al. 2006). Given the evidence that gut dysbiosis may lead to the activation of gut immune systems and subsequent low-grade inflammation of the gut (Ohman and Simren 2010), it is likely that microbes residing in the gut play a role in the pathogenesis of IBS. In this context, notwithstanding the huge variations in the gut microbial composition of patients with IBS (Ohman et al. 2015; Chong et al. 2019; Hugerth et al. 2020), there are some common features in IBS, including an increase in the families Enterobacteriaceae and Lactobacillaceae and a decrease in the genera *Clostridium, Faecalibacterium*, and *Bifidobacterium*, as compared with controls (Pittayanon et al. 2019). Interestingly, alterations in the microbial composition of patients with IBS include enrichment of certain types of typical oral bacteria in the gut. For example, *Streptococcus* spp. have repeatedly been reported to be enriched in the gut of patients with IBS (Wyatt et al. 1988; Kassinen et al. 2007; Rajilic-Stojanovic et al. 2011; Vich Vila et al. 2018). Likewise, an increased abundance of the family Veillonellaceae in the gut is often observed in IBS (Table 1). In this regard, overweight patients with IBS who have significantly higher IVP (induced visceral pain) scores exhibit a higher abundance of Veillonellaceae than normal-weight patients with IBS. Also, infants with colic—characterized by gastrointestinal discomfort caused by the accumulation of lactate, hydrogen (H_2), or hydrogen sulfide (H_2S)—have an increased level of Veillonellaceae in the gut (Pham et al. 2017). The ability of *Veillonella* spp. to produce a robust quantity of H_2 suggests that *Veillonella* spp. may play a role in determining the pathogenesis of IBS.

Inflammatory Bowel Disease

IBD is an idiopathic disorder that causes chronic inflammation of the digestive tract, comprising Crohn's disease (CD) and ulcerative colitis. Imbalance of the gut microbiota appears to be an essential factor in the pathogenesis of IBD (Sartor 2008). Multiple studies have shown the difference in the gut microbial composition between patients with and without IBD (i.e., healthy individuals; Lloyd-Price et al. 2019). Gut dysbiosis in IBD is characterized by a decrease in the bacterial diversity and species richness of the microbiota. In this context, one large multicenter microbiome study involved the collection of >400 treatment-naïve pediatric CD samples from multiple concurrent gastrointestinal sites (e.g., stool, rectal, ileum). The results clearly demonstrated a significant correlation between microbial alterations in rectal and ileal mucosa and disease status,

Table 1. Oral Bacteria Found in the Gut of Patients with Gut Pathology.

Gut Pathology: Oral Bacterial Species Detected in the Gut[a]	Sample Type	Percentage Abundance in Healthy Individuals			
		Saliva	Gingiva	Buccal	Stool
Irritable bowel syndrome					
Streptococcus (genus)	Stool	13.94	10.04	51.49	0.04
Streptococcus thermophilus	Stool	2.63[b]	0.10[b]	1.92[b]	0.01[b]
Veillonella (genus)	Stool	11.64	3.91	3.35	0.08
Haemophilus (genus)	Stool	12.65	4.06	15.12	0.07
Prevotella (genus)	Stool	13.01	8.79	2.27	3.4
Fusobacterium (genus)	Stool	6.42	13.75	2.54	0.06
Dialister invisus	Stool	0.17	0.38	0.04	0.67
Gammaproteobacteria (class)	Stool	13.7	6.13	15.89	0.24
Enterobacteriaceae (family)	Stool	0.01	<0.005	<0.005	0.01
Inflammatory bowel disease					
Veillonellaceae (family)	Tissue	12.7	4.5	3.47	0.94
Pasteurellaceae (family)	Tissue	13.61	5.83	15.83	0.07
Neisseriaceae (family)	Tissue	6.57	6.07	3.34	<0.005
Peptostreptococcaceae (family)	Tissue	0.51	0.52	0.08	0.11
Atopobium parvulum	Tissue	0.42	0.05	0.06	<0.005
Fusobacteriaceae (family)	Stool, tissue	6.42	13.75	2.54	0.06
Fusobacterium varium	Tissue	<0.005	ND	ND	0.02
Campylobacter (genus)	Tissue	1.93	0.99	0.2	<0.005
Campylobacter concisus	Stool, tissue	1.66	0.1	0.01	<0.005[b]
Aggregatibacter segnis	Stool	0.11	0.27	0.02	<0.005
Streptococcus (genus)	Stool, tissue	13.94	10.04	51.49	0.04
Streptococcus anginosus	Stool	<0.005[b]	0.02[b]	0.05[b]	<0.005[b]
Gemellaceae (family)	Stool, tissue	0.87	0.53	6.32	<0.005
Enterobacteriaceae (family)	Stool, tissue	0.01	<0.005	<0.005	0.01
Escherichia coli	Stool, tissue	0.01[b]	<0.005	<0.005[b]	<0.005
Colorectal cancer					
Porphyromonas (genus)	Stool, rectal swab	4.67	3.6	2.66	<0.005
Porphyromonas gingivalis	Stool	<0.005	0.01	<0.005	<0.005
Porphyromonas uenonis	Stool	ND	ND	ND	ND
Fusobacterium (genus)	Tissue, rectal swab	6.42	13.75	2.54	0.06
Fusobacterium nucleatum	Stool	0.78	8.45	0.38	<0.005
Streptococcus (genus)	Stool	13.94	10.04	51.49	0.04
Peptostreptococcaceae (family)	Stool, rectal swab	0.51	0.52	0.08	0.11
Peptostreptococcus stomatis	Stool	0.3	0.08	0.05	<0.005
Peptostreptococcus anaerobius	Stool	<0.005	<0.005[b]	<0.005[b]	<0.005
Prevotella (genus)	Stool	13.01	8.79	2.27	3.4
Prevotella intermedia	Stool	0.13	0.66	0.04	ND
Gemella morbillorum	Stool, rectal swab	0.87[b]	0.53[b]	6.32[b]	<0.005[b]
Solobacterium moorei	Stool	0.01	<0.005	<0.005	<0.005
Atopobium parvulum	Stool	0.42	0.05	0.06	<0.005
Actinomyces odontolyticus	Stool	1.43	0.16	0.49	<0.005
Parvimonas micra	Stool	0.16	0.51	0.05	<0.005
Escherichia coli	Stool, tissue	0.01[b]	<0.005	<0.005[b]	<0.005
Klebsiella (genus)	Stool	<0.005	<0.005	<0.005	<0.005
Helicobacter pylori	Tissue	<0.005	<0.005	<0.005	<0.005
Mogibacterium	Stool	0.15	0.03	0.02	<0.005
Dialister pneumosintes	Tissue	0.04	0.07	0.01	<0.005
Celiac disease					
Staphylococcus (genus)	Stool	0.01	0.01	0.01	0.19
Staphylococcus epidermidis	Tissue	0.01[b]	0.01[b]	0.01[b]	0.19[b]
Enterobacteriaceae (family)	Tissue	0.01	<0.005	<0.005	0.01
Klebsiella oxytoca	Tissue	<0.005[b]	<0.005[b]	<0.005[b]	<0.005[b]

ND, not detected.

[a]The taxonomic rank is provided in parentheses only if the species information is not defined in the reference. Oral bacteria are defined per the following criteria: 1) bacteria identified as a constituent of the oral microbiome by the Human Oral Microbiome Database (Escapa et al. 2018) and 2) bacteria having higher abundance in the oral tissues than in the gut samples. The percentage abundance in the saliva, gingiva, buccal mucosa, and stool in healthy individuals, based on the NIH Human Microbiome Project (HMP1), is shown. In addition, some bacteria that were previously reported as bacteria involved in oral pathology are listed as possible oral bacteria even if they do not meet criterion 2. References are provided in Appendix Table 1.

[b]Amplicon sequence variants also match some other taxa (likely in the same genus).

with an increased abundance of Veillonellaceae, Pasteurellaceae, Enterobacteriaceae, Nisseriaceae, Gemellaceae, and Fusobacteriaceae and a decreased abundance of Bacteroidales, Erysipelotrichales, and Clostridiales (Gevers et al. 2014). Notably, most of the bacteria enriched in the gut of these pediatric patients with CD were resident oral bacteria rather than typical resident bacteria in the gut, implying the contribution of oral bacteria to the pathogenesis of CD. Enterobacteriaceae are generally considered gut bacteria but not typical oral bacteria. However, a recent study showed that Enterobacteriaceae that reside in the saliva can elicit pathogenic immune responses when they ectopically colonize the gut (Atarashi et al. 2017). In this study, members of the family Enterobacteriaceae, in particular *Klebsiella* spp. (*K. pneumoniae* and *K. aeromobilis* [also known as *K. aerogenes*]), were isolated from gnotobiotic animals colonized by salivary microbiota derived from patients with IBD and identified as potent Th1 inducers in the gut. These *Klebsiella* strains are capable of eliciting severe gut inflammation when colonized in hosts genetically susceptible to IBD. Although Enterobacteriaceae, including *Klebsiella* spp., are only a minor constituent of oral microbiota, multiple studies reported that Enterobacteriaceae, including *Klebsiella* and *E. coli*, reside in the oral cavity in humans (Souto 2006; Baek et al. 2018; Zawadzki et al. 2016). Thus, at least a part of Enterobacteriaceae enriched in the gut of patients with CD could also be originated from the oral cavity (Table 1).

Colorectal Cancer

The colon is exposed to an infinite number of microorganisms, corresponding to about 70% of the estimated human microbiome (Sekirov et al. 2010). Given that most of the known colon cancer risks (e.g., age, inflammation, obesity) are closely associated with gut dysbiosis, it is conceivable that certain gut microbes contribute to tumor cell generation, by directly or indirectly shaping a microenvironment in the gut that is more favorable to tumor development. Many studies have shown that patients with CRC have a distinct gut microbial composition as compared with healthy individuals (Table 1). Of note, many of the bacteria enriched in colonic adenomas and carcinomas are related to the typical resident oral bacteria, including the families Streptococcaceae and Neisseriaceae and the genera *Staphylococcus, Porphyromonas, Veillonella*, and *Fusobacterium* (Kostic et al. 2013; Geng et al. 2014). This observation received validation from 3 recent large cohort studies demonstrating reproducible CRC-associated gut microbial signatures (Thomas et al. 2019; Wirbel et al. 2019; Yachida et al. 2019). These studies showed that patients with CRC have an enrichment of members of the oral microbes, including *Fusobacterium, Atopobium, Actinomyces, Parvimonas, Peptostreptococcus, Porphyromonas*, and *Solobacterium*, in the gut (Table 1). Furthermore, patients diagnosed with CRC had higher transmission rates of bacteria from the mouth to the gut when compared with healthy individuals. In particular, the transmission of *Fusobacterium nucleatum, Parvimonas micra*, and *Peptostreptococcus stomatis* was increased in patients with CRC. These results likewise support a potential link between the oral and gut microbiome in the context of CRC (Schmidt et al. 2019).

Mechanistic Insights into the Role of Oral Bacteria in Gut Pathology

Despite increasing knowledge of oral bacterial dissemination to the gut, the functional role of oral bacteria in the development of intestinal pathology remains unexplored. Published reports demonstrate plausible molecular mechanisms by which oral bacteria affect the host responses to enhance diseases of the gut. The mechanistic role of 3 bacteria are discussed in turn and summarized in Table 2.

Fusobacterium nucleatum

F. nucleatum is enriched in the colonic mucosa of patients with IBD and CRC (Table 1). A recent study showed that identical strains of *F. nucleatum* are detected in both the saliva and colonic tumors of patients with CRC, indicating that *F. nucleatum* colonized in the colonic tumors originates in the oral microbiota (Komiya et al. 2019). Unlike other oral bacteria, the mechanistic role of *F. nucleatum* has been relatively well explored. *F. nucleatum* is highly adhesive to the gut epithelium through Fap2 adhesin–mediated binding to Gal-GalNAc (galactose *N*-acetyl-D-galactosamine; Abed et al. 2016). Reports that *F. nucleatum* promotes the proliferation of tumor cells in vitro and in vivo may be explained by the *F. nucleatum* FadA adhesin–mediated activation of the Wnt/β-catenin pathway (Rubinstein et al. 2013). Furthermore, *F. nucleatum* plays a pivotal role in controlling CRC chemoresistance in response to chemotherapy drugs (e.g., oxaliplatin) by selectively targeting miRNAs and activating the autophagy pathway (Yu et al. 2017). Beyond a direct interaction with epithelial cells, *F. nucleatum* can shape the tumor microenvironment by altering the cytotoxic functions of tumor-infiltrating lymphocytes and natural killer cells. This action is mediated by the interaction between the inhibitory immunoreceptor TIGIT on these immune cells and Fap2 (Gur et al. 2015). Given that the overrepresentation of *Fusobacterium* in CRC positively correlates with lymph node metastasis, *Fusobacterium* spp. may have further malignant potential that needs to be clarified. Notably, the ectopic gut colonization by fusobacteria can be a biomarker for the detection of CRC. A recent study reported that the fecal abundance of fusobacteria in combination with that of the potentially beneficial populations (e.g., *Bifidobacterium*) might serve as a biomarker for early CRC (Guo et al. 2018). Also, measuring anti-Fn-IgA level with the conventional biomarkers, such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen, may increase the sensitivity for the detection of early CRC (Wang et al. 2016).

Porphyromonas gingivalis

P. gingivalis accumulates in the gut of patients with CRC. Although the precise role of *P. gingivalis* in the pathogenesis of CRC remains unknown, some pathologic functions of

Table 2. Possible Mechanisms of Oral Bacteria in the Gut Pathogenesis.

Oral Bacteria: Target Cells	Effector	Pathways in Host Cells		Pathologic Functions
		Receptor	Related Signals	
Fusobacterium nucleatum				
Epithelial cells	Fap2	Gal-GalNAc		Tumor binding and enrichment
Epithelial cells			Metalloproteinase collagenase	Cellular migration and invasive properties
Epithelial cells	FadA	Ecad	Wnt/β-catenin	Tumor cell proliferation
NK cells, T cells	Fap2	TIGIT		Immune evasion
Epithelial cells	LPS	TLR4	miR-4802, miR-18a*	Chemoresistance (autophagy activation)
Epithelial cells	LPS	TLR4	Myd88, miR-21	Tumor cell proliferation Recruitment of tumor-infiltrating immune cells (MDSC, TAM, regDC)
Fusobacterium varium epithelial cells				Adhesion and invasion, IL-8 and TNF-α production
Porphyromonas gingivalis				
Epithelial cells			Jak1/Akt/Stat3, PI3K/Akt	Cell survival (antiapoptotic)
Epithelial cells			Cyclin D and E, PI3K	Cell proliferation
Epithelial cells	Gingipain	β-catenin destruction, complex degradation	β-catenin	Cell proliferation
Epithelial cells				Immune evasion (B7-H1 and B7-DC upregulation)
Epithelial cells	Gingipain	PAR	NF-kB, ERK1/2, p38	Tumor invasiveness (MMPs expression↑)
Epithelial cells and others				Epithelial disruption, proinflammatory cytokine induction, gut dysbiosis
Epithelial cells and others				Epithelial disruption, immune activation, gut dysbiosis
Neutrophils		TLR1-TLR2	Myd88	Impaired antimicrobial response, Impaired killing activity
Mø and DC	Fimbrial proteins (FimA and Mfa1)	CR3 or DC-SIGN	MMP and C1q	Hijack and direct host immune cells (distant tissue destruction)
Klebsiella pneumoniae, K. aerogenes (K. aeromobilis) epithelial cells		TLR	*IL18* and Myd88	Th1 cell generation
Atopobium parvulum: unknown	H_2S			Mitochondrial dysfunction in host with impaired H_2S detoxification
Campylobacter concisus epithelial cells				Epithelial disruption
Staphylococcus aureus epithelial cells, T cells	Enterotoxins			Epithelial disruption, immune activation

P. gingivalis implicate a pathogenic role for this bacterium in CRC (Table 2). For instance, oral administration of *P. gingivalis* to mice is reported to disrupt the gut epithelial integrity (e.g., reduced expression of tight junction proteins; Arimatsu et al. 2014; Nakajima et al. 2015). *P. gingivalis* also inhibits epithelial apoptosis through multiple mechanisms, including activation of the JAK1/STAT3 and PI3K/Akt signaling pathways (Yilmaz et al. 2004; Mao et al. 2007), inactivation of caspase 3 and 9 (Mao et al. 2007; Yao et al. 2010), and prevention of P2X7-mediated apoptosis (Yilmaz et al. 2008). Similar to *F. nucleatum, P. gingivalis* is capable of potentiating epithelial cell proliferation through activation of the Wnt/β-catenin pathway (Zhou et al. 2015), as well as by controlling the activity of PI3K, p53, and cyclins (Kuboniwa et al. 2008; Pan et al. 2014). Furthermore, *P. gingivalis* contributes to the invasive properties of tumors through the activation of matrix metalloproteinases (MMPs), including MMP-1, MMP-9, MMP-10, and MMP-13 (Inaba et al. 2014; Ha et al. 2015; Inaba et al. 2015). Also, *P. gingivalis* is known to invade macrophages and dendritic cells through the interaction between its fimbrial proteins and complement receptor 3 (or DC-SIGN) on the immune cell surface. After hijacking the immune cells, *P. gingivalis* instigates the production of proteins that destroy tissue, such as MMP-9, from the infected cells. The role that MMPs play in controlling the invasive properties of tumors suggests that oral bacteria residing in colonic tumors may contribute to the metastatic potential of these tumors (Hajishengallis 2015).

Klebsiella *Species*

A recent study showed that the colonization of germ-free mice with salivary microbiota isolated from patients with CD resulted in potent Th1 cell differentiation in the gut (Atarashi et al. 2017). In this study, the authors determined that certain *Klebsiella* spp. (e.g., *K. pneumoniae, K. aerogenes/aeromobilis*) residing in the salivary microbiota are responsible for the induction of Th1 cells. Interestingly, the expansion of Th1 cells due to the ectopic gut colonization by oral *Klebsiella* spp. does not lead to the development of spontaneous gut inflammation. However, these oral *Klebsiella* spp. are capable of inducing the development of Th1-skewed IBD-like colitis in mice lacking the immunosuppressive cytokine IL-10. Given that impaired IL-10 signaling is associated with the risk for very-early-onset IBD (Moran et al. 2013), oral bacteria such as *Klebsiella* spp. may contribute to the pathogenesis of certain subsets of IBD.

Other Oral Bacteria

Members of the oral microbiota found in the gut are known to produce carcinogenic substances. Similar to *F. nucleatum* and *P. gingivalis*, certain types of oral bacteria (e.g., *Atopobium* spp., *Veillonella* spp., *Prevotella* spp., *Streptococcus* spp., and *Aggregatibacter* spp.) are known to liberate H_2S, a genotoxic and inflammatory substance, from sulfur-containing amino acids. Also, many species of indigenous oral bacteria, such as *Streptococcus* spp. and *Neisseria* spp., have been reported to produce acetaldehyde by catabolizing ethanol and glucose (Tagaino et al. 2019). Given the high genotoxic capacity of these bacterial metabolites, even at low concentrations, it is conceivable that ectopic colonization of the gut by these oral bacteria could induce genomic instability or mutations, leading to colonic tumor development.

Possible Pathways of Ectopic Gut Colonization by Oral Bacteria

Although the mode of the relocation of oral bacteria from the oral cavity to the gut mucosa is uncertain, 2 routes have been proposed: hematogenous and enteral.

Hematogenous Route

One possible route of oral bacteria dissemination is by hematogenous spreading from the oral cavity (Fig.). Studies have shown that oral mechanical injuries caused by daily dental activity (e.g., hard mastication, brushing) and dental procedures (e.g., orthodontics, extraction) enable oral bacteria to spread into the systemic circulation (Lockhart et al. 2008; Parahitiyawa et al. 2009). Patients with periodontal diseases such as periodontitis and oral cancer have an elevated level of oral bacteria in their blood. Moreover, a ligature-induced murine periodontitis model showed that periodontal inflammation triggers oral bacterial dissemination to the liver and spleen, indicating a key role for oral inflammation in the systemic dissemination of oral bacteria through the bloodstream (Tsukasaki et al. 2018). This role was supported by another study that identified periodontal pathogens such as *P. gingivalis* in the bloodstream of patients with periodontitis (Horliana et al. 2014). Furthermore, as described in Table 2, oral bacteria is known to invade and survive inside immune cells, such as dendritic cells and macrophages, indicating that oral bacteria may hijack host immune cells to serve as Trojan horses for dissemination from the oral mucosa to the gut mucosa (Hajishengallis 2015).

Enteral Route

Another possible route of oral bacteria dissemination is by enteral spreading. People swallow about 600 times a day, and ~1.5 L of saliva contains numerous resident oral bacteria (Humphrey and Williamson 2001; Pedersen et al. 2002). However, ingested oral bacteria seldom reach and colonize the healthy gut because of the barrier functions along the gastrointestinal tract. The colonization resistance by the gut resident microbiota is considered the major barrier that prevents the ectopic colonization by swallowed oral bacteria. In other words, the disruption of the healthy gut microbiota results in the increased gut colonization by oral bacteria (Fig). For instance, antibiotics (e.g., vancomycin) used to treat bacterial infections are known to perturb gut microbial composition and to generate niches for translocated oral bacteria to colonize and expand in the gut. Th1 cell–inducing *Klebsiella* spp. that reside in the saliva of patients with IBD possess resistance to multiple antibiotics, including ampicillin (Atarashi et al. 2017). Hence, ampicillin treatment can result in the gut colonization by oral *Klebsiella* spp. and subsequent pathogenic Th1 cell expansion in the gut, suggesting that inadequate use of antibiotics may increase the risk for oral bacteria–driven gut pathology (Atarashi et al. 2017). Other than the aforementioned gut dysbiosis–inducing factors, multiple factors that elicit gut dysbiosis (e.g., gut inflammation, diets, artificial sweeteners) may increase the opportunistic gut colonization by oral bacteria. Considering all these factors, gut dysbiosis may be a prerequisite for the ectopic colonization of oral pathobionts.

Also, gastric acidity is an important bottleneck for oral bacteria. Since the majority of oral resident bacteria are sensitive to the gastric acid, ingested oral bacteria might be significantly reduced while they are passing the stomach. Consistent with this notion, patients who have gastric dysfunction related to achlorhydria caused by the long-term use of proton pump inhibitors exhibit a significant increase in gut colonization by oral bacteria (e.g., *Streptococcus* spp., *Veillonella* spp., *Haemophilus* spp.; Fig.). Another example of reduced exposure of ingested bacteria to gastric juice may occur in individuals who have gastritis and gastric surgery (e.g., gastric bypass and removal; Castaner et al. 2018; Paganelli et al. 2019). These individuals have an altered gut microbial composition, accompanied by a significant increase in the level of resident oral bacteria (e.g., *Streptococcus* spp., *Veillonella* spp., and

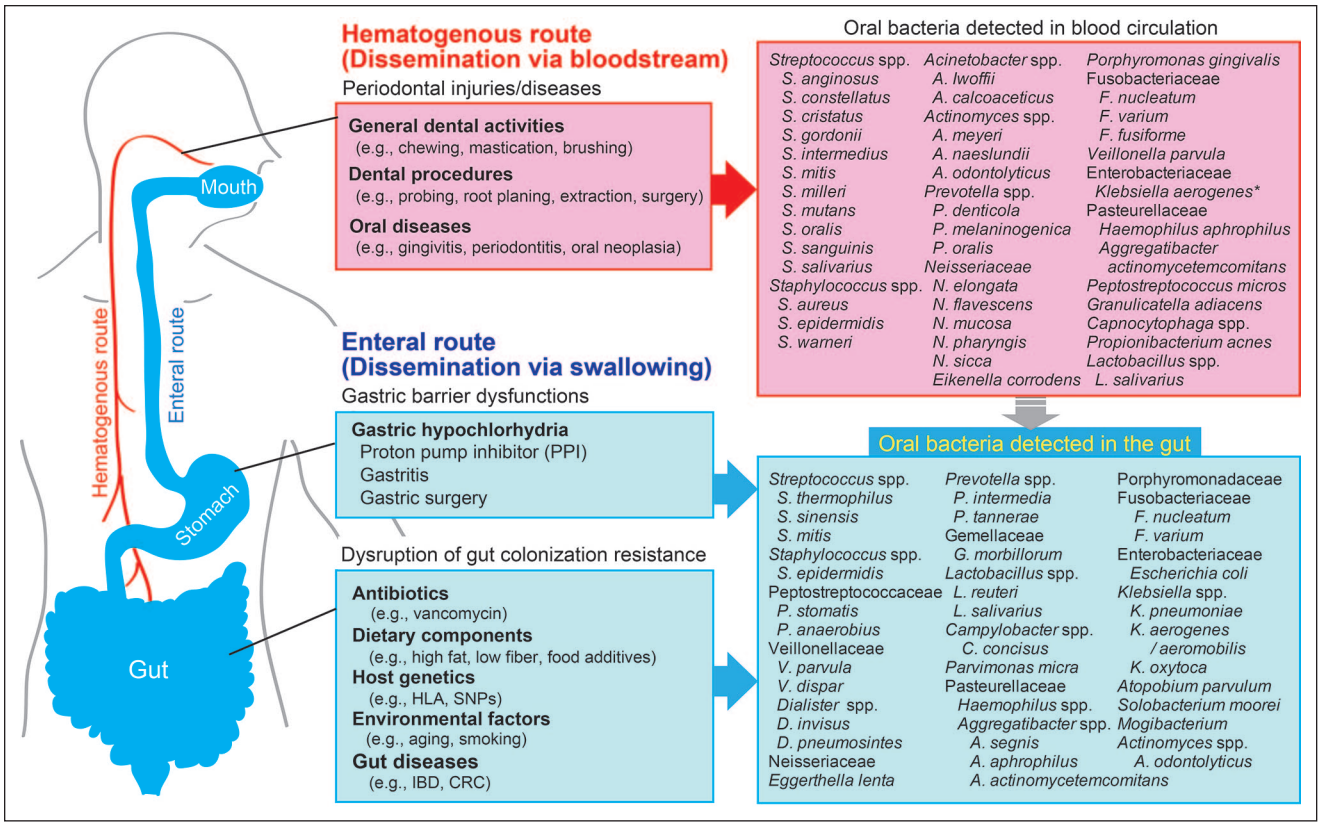

Figure. Possible routes of oral bacteria transmigration from the mouth to the gut. The diagram depicts possible routes of oral bacteria transmigration from the oral cavity to the gut and potential factors contributing to the ectopic colonization of oral bacteria in the gut. Laboratory and clinical studies discussed in this review reveal 2 possible routes: hematogenous (red) and enteral (blue). **Enterobacter aerogenes* was renamed *Klebsiella aerogenes* in 2017.

Enterobacteriaceae) in the gut. Interestingly, certain types of oral bacteria, such as *P. gingivalis*, are able to tolerate the harsh acidic environment in the stomach and consequently may pass through the stomach barrier (Walker et al. 2018). Thus, gastric acidity can prevent the enteral transmission of oral bacteria but might be less effective for bacteria that are tolerated to the acidic environment.

Other Possible Factors Associated with the Ectopic Colonization of Oral Bacteria

In addition to the aforementioned mechanisms, other factors may be responsible for the ectopic colonization of oral bacteria. For example, immune-compromised individuals (e.g., patients infected with HIV) have gut dysbiosis accompanied by the accumulation of oral bacteria, such as the Prevotellaceae, Erysipelotrichaceae, and Veillonellaceae families and the Proteobacteria phylum (Crakes and Jiang 2019). Given the importance of host immunity in shaping gut microbiota composition and its colonization resistance, it is likely that immune depression by multiple factors (e.g., aging, drugs, virus infection) may promote the ectopic gut colonization by oral bacteria. Furthermore, overgrowth of oral pathogenic bacteria in the diseased oral cavity may increase the supply of oral bacteria, resulting in increased oral bacterial colonization in the gut. For instance, periodontal pathogens such as *F. nucleatum* and *P. gingivalis* expand in the oral cavity of patients with periodontitis (Socransky et al. 1998). Notably, a recent large cohort study (n = 77,443) revealed that women with fewer teeth and presumably moderate or severe periodontal inflammation have up to a 48% increased risk for developing CRC (Momen-Heravi et al. 2017). Given the high prevalence of certain periodontal pathogens in the gut of individuals with CRC (Table 1), it is conceivable that poor oral health, accompanied by the expansion of certain oral bacteria, may cause an oversupply of the oral bacteria to the gut, increasing the chance of oral bacterial colonization in the gut. However, only a few studies have focused on the link between periodontal disease and gut pathology. Further large cohort studies are needed to clarify the clinical relevance of periodontal disease in the development of gut pathology.

Conclusions and Perspective

Considering the results of many investigations, the mouth-to-gut transmission may be an important process in bacteria-driven pathologies in the gastrointestinal tract. However, as mentioned, most of the studies demonstrating the pathologic

link between oral bacteria and extraoral diseases are observational and still at the stage of association. There is a need for more studies to elucidate the transmigration mechanisms of oral bacteria to extraoral sites and to understand the precise role of oral pathobionts in the pathogenesis of diseases at extraoral sites, including the gastrointestinal tract. In parallel and also essential are further epidemiologic cohort studies to clarify the clinical relevance of oral pathology, accompanied by the expansion of oral pathobionts, in the development of gut pathology. These efforts will pave the way for the future development of novel diagnostic and therapeutic interventions to target oral bacteria.

Author Contributions

S. Kitamoto, H. Nagao-Kitamoto, contributed to conception and design, drafted the manuscript; R. Hein, T.M. Schmidt, contributed to conception, design, and data analysis, drafted the manuscript; N. Kamada, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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