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The microbiome and gastric carcinogenesis

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Abstract: Gastric cancer occurs in a small group of patients following chronic infection with *Helicobacter pylori*. The development of gastric cancer is multifactorial. Current knowledge that a complex microbial community inhabits the stomach has raised the hypothesis that bacteria other than *H. pylori* may play a role in gastric carcinogenesis. In this paper, we summarize recent results of the characterization of the microbiota at different sites of the gastrointestinal tract, including the stomach. We also review the latest evidence from human studies and from animal models addressing the role of the gastric microbiota in gastric carcinogenesis. Finally, we highlight recent reports that explore the oral and the gut microbiota as potential gastric cancer biomarkers.

Keywords: Microbiome, Gastric cancer, Stomach, Gastrointestinal tract, *Helicobacter pylori*.

BACKGROUND

The discovery of *Campylobacter pylori* (later renamed *Helicobacter pylori*) in 1983 by Marshall and Warren[1] revolutionized the diagnosis and treatment of gastric diseases and broke the dogma that the human stomach was sterile. These findings opened a new chapter of research on infectious diseases of the upper gastrointestinal (GI) tract, and substantial knowledge on the pathophysiology of *H. pylori* infection has meanwhile accumulated. At present, with the development of culture-independent and high-throughput sequencing methods, we are aware of the existence of a complex bacterial community in the stomach, with distinct compositions in mucosa and lumen, and that differs from communities of other sites of the GI tract[2-5].

THE GASTRIC MICROBIOTA

A common issue of debate is whether the gastric microbiota has its own niche or is constituted by a transient population. In an attempt to clarify this aspect, Schulz et al[5] characterized the microbiota of saliva and of both aspirates and biopsies from the stomach and duodenum from 24 patients, by sequencing 16S rRNA transcripts. While no significant differences were detected in the structure or composition (at phylum or genus level) of the oral microbial communities between *H. pylori*-infected and non-infected individuals, the authors demonstrated significant differences between the gastric luminal and gastric mucosal bacterial communities, in both *H. pylori*-infected and non-infected individuals. This suggests that rather than representing transient swallowed microorganisms, the adherent microbiota is selected by the gastric mucosal environment.

Additional insights into the microbial community of the stomach have been provided by recent studies that characterized the microbiota of the same individuals at different sites of the GI tract[6-8]. Vuik et al[6] analysed the mucosal microbiome from nine different sites of the GI tract in 14 subjects. The analyses, based on 16S rRNA gene sequencing, demonstrated significant differences in diversity between the upper (distal oesophagus, gastric antrum, proximal and distal duodenum, proximal ileum) and lower GI tract (distal ileum, ascending and descending colon, and rectum), the latter with higher microbial diversity. Firmicutes, Proteobacteria, and Bacteroidetes were the main phyla, but their profile changed along the GI tract, with Proteobacteria and Firmicutes dominating the mucosal microbiota of the upper GI, and Firmicutes and Bacteroidetes dominating the microbiota of the lower GI tract. *Veillonellaceae*, *Pseudomonadaceae*, *Streptococcaceae*, *Prevotellaceae*, and *Helicobacteraceae* were the most prevalent bacterial families in the gastric antrum. *Helicobacter* species were detected at low abundances in nine individuals in various locations, mostly on the upper GI tract.

Mailhe et al[7] also reported significant differences in the bacterial composition and diversity along different sites of the GI tract, when characterizing samples from six patients using culturomics with MALDI-TOF in combination with 16S rRNA gene sequencing. Overall, they isolated 368 different species of bacteria, 37 of which were new species. The highest number of species was isolated from the lower GI tract, and 110 species were isolated from the stomach, including three novel species, *Actinomyces bouchesdurhonensis*, *Bacteroides mediterraneensis*, and *Streptococcus timonensis*. In agreement with Vuik et al[6], the upper GI microbiota was less rich than the lower GI microbiota, with species from the phyla Firmicutes, Proteobacteria, and Bacteroidetes dominating.

Vasapolli et al[8] undertook an approach to identify transcriptionally active bacterial microbiota in saliva, in mucosal samples from the upper (gastric corpus and antrum, and duodenum) and lower GI tract (terminal ileum, and ascending and descending colon), and in faecal samples from 21 healthy subjects. Overall, the microbial profiles clustered into two groups, those that comprised bacterial communities from saliva and the upper GI tract, and the other that contained bacterial communities from the lower GI tract and faeces, and that showed a higher level of heterogeneity. The structure of the microbial communities had clear differences between the upper and lower GI tract, but no major differences were reported between the distinct sites within the upper or within the lower GI tract. In agreement with other reports that have used different technical approaches[6,7], Firmicutes, Bacteroidetes, and Proteobacteria were dominant. In the stomach, *Streptococcus, Pseudomonas, Prevotella,* and *Helicobacter* were the most abundant genera. In addition to the stomach, metabolically active *H. pylori* was detected at low levels in the duodenum but was virtually absent in the lower GI tract, as well as in faecal samples. Importantly, the authors demonstrated that faecal samples did not reflect metabolically active bacterial communities from mucosal niches of the lower GI tract.

GASTRIC CARCINOGENESIS

Gastric cancer is still one of the cancers with highest incidence and mortality worldwide[9]. *H. pylori* is classified as carcinogenic to humans and is the infectious agent that contributes to the highest number of new cases of cancer[10]. Yet, and despite the recognized evidence on the association between *H. pylori* and gastric cancer, the majority of patients infected with *H. pylori* will not develop cancer. In addition to *H. pylori* infection, it is currently accepted that the virulence of the infecting *H. pylori* strain, together with the host genetic susceptibility, and various lifestyle factors, influence the disease outcome[11]. Recent data from clinical studies and from animal models of infection suggest that the non-*H. pylori* gastric microbiota may also play a role in gastric cancer development, and this has been recently reviewed[12-15].

THE GASTRIC MICROBIOTA IN GASTRIC CARCINOGENESIS

In the last year, two large studies compared the gastric microbiota between groups of patients with different histological stages of the gastric carcinogenesis cascade[16,17]. In a study comprising 135 patients (81 with chronic gastritis and 54 with gastric cancer) from Portugal, Ferreira et al[16] showed a significant decrease in microbial diversity from chronic gastritis to gastric cancer.

Among the genera that best explained differences between chronic gastritis and gastric cancer patients, they identified *Helicobacter* and *Neisseria* that had decreased abundance, and *Citrobacter*, *Lactobacillus*, and *Clostridium* that had increased abundance in the gastric cancer microbiota. When differentially abundant taxa were combined into a microbial dysbiosis index, they could distinguish the two patient groups in the receiver operating characteristic (ROC) analysis. Interestingly, the gastric cancer microbiota had increased nitrosating functional features, an aspect that is compatible with a microbial community with increased genotoxic potential. Of note, the results were confirmed by quantitative polymerase chain reaction and validated in cohorts from different geographic origins.

In a study that included 81 patients (21 superficial gastritis, 23 atrophic gastritis, 17 intestinal metaplasia, and 20 gastric cancer) from Xi'an, in China, Coker et al[17] showed significant decreases of gastric microbial richness in patients with intestinal metaplasia and gastric cancer, compared to patients with superficial gastritis. They identified *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes* as being enriched in the gastric microbiota of cancer patients, as central in the gastric cancer microbial interaction network, and as able to distinguish gastric cancer from superficial gastritis in ROC analysis. Importantly, these results were successfully validated in an Inner Mongolian patient cohort.

Liu et al[18] demonstrated that the structure and composition of the gastric microbiota of cancer patients differ across different gastric microhabitats. In a study of 276 Chinese patients with gastric cancer, they showed that microbial richness significantly decreased from normal gastric tissue, to the area in the periphery of the tumour, to the tumour tissue. While in the tumour tissues there was an enrichment of *Prevotella melaninogenica, Streptococcus anginosus*, and *Propionibacterium acnes,* and a decreased abundance of *H. pylori*, in the normal and peritumoral areas, *H. pylori* influenced the overall structure of the microbiota. Furthermore, the microbiota from the three gastric microhabitats had different bacterial correlation networks and functions. Specifically, the microbiota in the tumour site showed a less complex network of interactions compared to that in the peritumoral and normal microhabitats and was significantly enriched in the predicted functional genes involved in the nucleotide transport and metabolism, and amino acid transport and metabolism.

Whether differences of the gastric microbiota in distinct stomach microhabitats have a role in gastric carcinogenesis or are a consequence of tumour evolution remains to be clarified.

Hu et al[19] conducted a whole metagenome sequencing (WMS) survey on the microbiome of gastric wash samples from six gastric cancer and five superficial gastritis patients and identified compositional and functional differences between clinical diagnoses. The microbial richness was significantly decreased in the gastric cancer microbiome, which was characterized by enrichment of commensals or opportunistic pathogens from the oral cavity, and by metabolic pathways of lipopolysaccharide and amino acid biosynthesis. So far, no reports have reliably performed WMS in gastric mucosal specimens. This is because in this type of specimens the amount of host DNA (> 96%) significantly reduces the sensitivity of WMS for microbiome profiling, in particular to detect very low and low abundant bacteria species[20].

Animal models have been pivotal in showing the importance of the microbiome in gastric carcinogenesis. In the transgenic insulin-gastrin (INS-GAS) mouse model that develops gastric intraepithelial neoplasia (GIN) seven months after *H. pylori* infection, Lofgren et al[21] showed that in comparison with *H. pylori*-infected INS-GAS mice harbouring a complex gastric microbiota, *H. pylori*-infected germ-free INS-GAS mice had less severe gastric lesions and delayed the onset of GIN. The importance of the microbiota in the promotion of gastric neoplasia has also been shown in the K19-Wnt1/C2mE (Gan) mouse model of gastric carcinogenesis, which has simultaneous activation of the Wnt and PGE_2 pathways[22]. Oshima et al[22] demonstrated that in contrast to Gan mice raised under specific pathogen-free conditions, which develop large gastric tumours by 55 weeks of age, in Gan mice raised under germ-free conditions gastric tumorigenesis is significantly suppressed. The authors also showed that the reconstitution of commensal bacteria in Gan germ-free mice or infection with *Helicobacter felis* resulted in development of gastric tumours.

It has been suggested that colonization of the stomach with commensal bacteria from other locations of the GI tract may promote *H. pylori*-associated gastric carcinogenesis. Using the INS-GAS mouse model, Lertpiriyapong et al[23] described that colonization of *H. pylori*-infected mice with a restricted intestinal microbiota (*Clostridium* spp., *Lactobacillus murinus*, and *Bacteroides* spp.), recapitulated the histopathological findings, and the incidence of GIN observed in *H. pylori*-infected INS-GAS mice harbouring a complex microbiota.

Although animal models are fundamental *in vivo* disease models, differences in the microbiome composition may constitute an important source of experimental variability. Ge et al[24] demonstrated that C57BL/6 (B6) mice from different vendors have significant differences in the structure of microbial communities along the GI tract, which likely explain the dissimilar responses to *H. pylori* infection. *H. pylori* infection had different efficiency of gastric colonization and different impact in the structures of the microbial communities of the stomach, colon, and faeces of B6 mice from different vendors. The pathological and immunological responses that animals from the two vendors developed in response to *H. pylori* infection were also different. These results are in agreement with those of Velazquez et al[25] who very recently reported that the differences in the microbiota composition in genetically similar mice from different commercial vendors were responsible for the divergent phenotypes of susceptibility to *Salmonella* infection. These results emphasize the importance of the microbiome in the reproducibility of animal experiments.

THE ORAL AND GUT MICROBIOTA IN GASTRIC CARCINOGENESIS

Several studies have explored the oral and the gut microbiomes in an attempt to identify microbial signatures that could be used as potential biomarkers for gastric cancer and precursor lesions. Sun et al[26] characterized the oral microbiome of saliva and of subgingival plaque in 37 patients with gastric cancer and 13 healthy controls. They found that the oral microbiome was more complex in gastric cancer patients, with significant enrichment of *Veillonella*, *Prevotella*, *Aggregatibacter*, and *Megasphaera* and decreased *Leptotrichia*, *Rothia*, and *Campylobacter*, in comparison to healthy controls. Based on a scoring system that included 11 oral microbiome species they could identify gastric cancer patients with a sensitivity rate of 97%.

Wu et al[27] also reported differences in the oral tongue coating microbiota between gastric cancer patients (n = 57) and healthy controls (n = 80) from China. The tongue coating microbiota of patients with gastric cancer had lower microbial richness, and clustered separately from that of healthy controls based on weighted Unifrac metrics. The authors identified six bacterial clusters, including a cluster with *Streptococcus* and *Abiotrophia* that was associated with gastric cancer, and a cluster containing *Prevotella* that had an inverse association with gastric cancer and the best discriminatory power in ROC analysis.

Cui et al[28] performed a metagenomics analysis of the tongue coating of 78 chronic gastritis (44 superficial gastritis, 11 atrophic gastritis, and 23 intestinal metaplasia) patients and 50 healthy individuals living in Beijing. They identified a significant increase in the relative abundance of *Campylobacter concisus* between patients with superficial gastritis and atrophic gastritis. However, differences in the structure, composition, and functions of the tongue coating microbiome were only reported between the whole group of chronic gastritis patients and healthy controls.

Yousseff et al[29] investigated the composition of the gut microbiota in stool samples of Finnish patients with tumours in different locations of the GI tract (pancreas, small intestine, colon, rectum, and stomach) and of 13 healthy individuals, and reported significant differences in the abundances of specific taxonomic groups. The relative abundance of *Enterobacteriaceae* was significantly enriched in stool samples from patients with tumours in the stomach and small intestine. Additional differences in the gut microbiota of gastric cancer patients in comparison with that of healthy controls included enrichment in *Ruminococcus* and *Subdoligranulum*, and depletion in *Lachnoclostridium* and *Oscillibacter.*

Qi et al[30] profiled the intestinal microbial communities in faecal samples from gastric cancer patients (n = 116) and healthy controls (n = 88) from the Shanxi Province, in China. Their results showed increased microbial richness in the intestinal microbiota of gastric cancer patients. Among the genera that best explained differences between the two groups, they identified *Enterobacteriaceae* taxa*, Lactobacillus,* and *Streptococcus* that were enriched, and *Lachnospiraceae* taxa and *Faecalibacterium* that were depleted in the gastric cancer gut microbiota. *Lactobacillus* and *Lachnospira* were central taxa in the gastric cancer patient gut microbial network, being negatively correlated to each other. Moreover, the combination of *Lactobacillus, Lachnospira, Streptococcus, Veillonella*, and *Tyzzerella_3* had good discriminatory power between gastric cancer and healthy controls with an area under the curve of 0.95 in ROC analysis.

Studies also analysed the gut microbiota of patients at different stages of the gastric carcinogenesis cascade. Microbiota profiling of faecal samples from 47 Chinese subjects with no disease (n = 7), gastritis (n = 18) and intestinal metaplasia (n = 22) revealed significant increases in the rel-

ative abundance of *Firmicutes* in gastritis and intestinal metaplasia *vs.* normal stomach, and in the relative abundance of Proteobacteria in intestinal metaplasia *vs.* normal or gastritis[31]. In a study of Japanese subjects with non-atrophic gastritis (n = 111), mild atrophic gastritis (n = 81), and severe atrophic gastritis (n = 34), Iino et al[32] identified significantly increased relative abundance of *Lactobacillus* in the faecal microbiota of individuals with severe atrophic gastritis.

Although the idea that profiling the oral or the gut microbiome as a non-invasive approach for gastric cancer screening is attractive, many factors still need to be controlled. For example, when assessing the oral microbiome, the site of sample collection is very important, as there is high heterogeneity in the microbial communities across distinct sites within the oral cavity[26,33,34]. Another aspect that still needs clarification is the extent to which *H. pylori* infection has an impact on the oral or gut microbiomes. Chua et al[35] demonstrated that individuals with gastric *H. pylori* infection have significant differences in the structure and composition of the oral microbiota in comparison with individuals that are *H. pylori*-negative. Schulz et al[5] also detected three phylotypes (*Propionibacterium acnes, Haemophilus*, and *Prevotella oris*) significantly more abundant in the saliva of *H. pylori*-negative compared to *H. pylori*-positive individuals. Additionally, *Treponema* was absent in saliva from *H. pylori*-negative subjects. Regarding the gut microbiota, Gao et al[31] could not detect differences in alpha- or beta-diversity of faecal samples between *H. pylori*-infected (n = 24) and non-infected (n = 23) subjects, but found a significant difference in the faecal microbial community structure of *H. pylori*-negative subjects *vs.* those with past infection, the latter showing reduction in the relative abundance of Bacteroidetes. Iino et al[32] also showed that *H. pylori* infection has an impact on the proportion of different species of *Lactobacillus* in the gut microbiota, in particular on *L. salivarius* and *L. acidophilus.* Additionally, the use of proton pump inhibitors (PPIs) affects the oral and gut microbiota, which was reported by Mishiro et al[36]. The microbiome composition of saliva, periodontal pocket fluid, and faecal samples from healthy volunteers had significant alterations before and after taking PPIs for a period of four weeks. In particular, after PPI usage, *Neisseria*, and *Veillonella* were depleted in saliva and *Leptotrichia* was enriched in the periodontal pocket fluid. The genus *Streptococcus* was significantly enriched in the faecal microbiome after PPI intake, as it had been repeatedly reported in previous studies[37,38].

KNOWLEDGE GAPS AND CONCLUSIONS

In spite of the recent progress in our understanding of the microbiome, the debate on whether the gastric microbiota is a cause or a consequence of gastric cancer development is still ongoing. Large studies of prospective nature that include patients at different stages of the gastric carcinogenesis cascade, and that are well controlled for the geographic origin and environmental exposures of the patients, will be fundamental to elucidate the role of the gastric microbiota in cancer progression. These studies should also take into consideration the characterization of microbiomes from other body sites, in particular the oral and faecal microbiomes, considering the perspective of using them as non-invasive approaches for gastric cancer screening.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

REFERENCES

1. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; 1: 1273-1275.
2. Bik EM, Eckburg PB, Gill SR, Nelson KE, Purdom EA, Francois F, Perez-Perez G, Blaser MJ, Relman DA. Molecular analysis of the bacterial microbiota in the human stomach. Proc Natl Acad Sci U S A 2006; 103: 732-737.
3. Li XX, Wong GL, To KF, Wong VW, Lai LH, Chow DK, Lau JY, Sung JJ, Ding C. Bacterial microbiota profiling in gastritis without Helicobacter pylori infection or non-steroidal anti-inflammatory drug use. PLoS One 2009; 4: e7985.

4. Andersson AF, Lindberg M, Jakobsson H, Backhed F, Nyren P, Engstrand L. Comparative analysis of human gut microbiota by barcoded pyrosequencing. PLoS One 2008; 3: e2836.
5. Schulz C, Schutte K, Koch N, Vilchez-Vargas R, Wos-Oxley ML, Oxley APA, Vital M, Malfertheiner P, Pieper DH. The active bacterial assemblages of the upper GI tract in individuals with and without Helicobacter infection. Gut 2018; 67: 216-225.
6. Vuik F, Dicksved J, Lam SY, Fuhler GM, van der Laan L, van de Winkel A, Konstantinov SR, Spaander M, Peppelenbosch MP, Engstrand L, Kuipers EJ. Composition of the mucosa-associated microbiota along the entire gastrointestinal tract of human individuals. United European Gastroenterol J 2019; 7: 897-907.
7. Mailhe M, Ricaboni D, Vitton V, Gonzalez JM, Bachar D, Dubourg G, Cadoret F, Robert C, Delerce J, Levasseur A, Fournier PE, Angelakis E, Lagier JC, Raoult D. Repertoire of the gut microbiota from stomach to colon using culturomics and next-generation sequencing. BMC Microbiol 2018; 18: 157.
8. Vasapolli R, Schutte K, Schulz C, Vital M, Schomburg D, Pieper DH, Vilchez-Vargas R, Malfertheiner P. Analysis of Transcriptionally Active Bacteria Throughout the Gastrointestinal Tract of Healthy Individuals. Gastroenterology 2019; 157: 1081-1092 e1083.
9. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941-1953.
10. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 2016; 4: e609-616.
11. Figueiredo C, Camargo MC, Leite M, Fuentes-Panana EM, Rabkin CS, Machado JC. Pathogenesis of Gastric Cancer: Genetics and Molecular Classification. Curr Top Microbiol Immunol 2017; 400: 277-304.
12. Li J, Perez Perez GI. Is There a Role for the Non-Helicobacter pylori Bacteria in the Risk of Developing Gastric Cancer? Int J Mol Sci 2018; 19.
13. Wang LL, Liu JX, Yu XJ, Si JL, Zhai YX, Dong QJ. Microbial community reshaped in gastric cancer. Eur Rev Med Pharmacol Sci 2018; 22: 7257-7264.
14. Hold GL, Hansen R. Impact of the Gastrointestinal Microbiome in Health and Disease: Co-evolution with the Host Immune System. Curr Top Microbiol Immunol 2019; 421: 303-318.
15. Pereira-Marques J, Ferreira RM, Pinto-Ribeiro I, Figueiredo C. Helicobacter pylori Infection, the Gastric Microbiome and Gastric Cancer. Adv Exp Med Biol 2019.
16. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Carneiro F, Machado JC, Figueiredo C. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. Gut 2018; 67: 226-236.
17. Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G, Wu WK, Wong SH, Chen Z, Sung JJY, Yu J. Mucosal microbiome dysbiosis in gastric carcinogenesis. Gut 2018; 67: 1024-1032.
18. Liu X, Shao L, Liu X, Ji F, Mei Y, Cheng Y, Liu F, Yan C, Li L, Ling Z. Alterations of gastric mucosal microbiota across different stomach microhabitats in a cohort of 276 patients with gastric cancer. EBioMedicine 2019; 40: 336-348.
19. Hu YL, Pang W, Huang Y, Zhang Y, Zhang CJ. The Gastric Microbiome Is Perturbed in Advanced Gastric Adenocarcinoma Identified Through Shotgun Metagenomics. Front Cell Infect Microbiol 2018; 8: 433.
20. Pereira-Marques J, Hout A, Ferreira RM, Weber M, Pinto-Ribeiro I, van Doorn LJ, Knetsch CW, Figueiredo C. Impact of Host DNA and Sequencing Depth on the Taxonomic Resolution of Whole Metagenome Sequencing for Microbiome Analysis. Front Microbiol 2019; 10: 1277.
21. Lofgren JL, Whary MT, Ge Z, Muthupalani S, Taylor NS, Mobley M, Potter A, Varro A, Eibach D, Suerbaum S, Wang TC, Fox JG. Lack of commensal flora in Helicobacter pylori-infected INS-GAS mice reduces gastritis and delays intraepithelial neoplasia. Gastroenterology 2011; 140: 210-220.
22. Oshima H, Hioki K, Popivanova BK, Oguma K, Van Rooijen N, Ishikawa TO, Oshima M. Prostaglandin E(2) signaling and bacterial infection recruit tumor-promoting macrophages to mouse gastric tumors. Gastroenterology 2011; 140: 596-607 e597.
23. Lertpiriyapong K, Whary MT, Muthupalani S, Lofgren JL, Gamazon ER, Feng Y, Ge Z, Wang TC, Fox JG. Gastric colonisation with a restricted commensal microbiota replicates the promotion of neoplastic lesions by diverse intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. Gut 2014; 63: 54-63.
24. Ge Z, Sheh A, Feng Y, Muthupalani S, Ge L, Wang C, Kurnick S, Mannion A, Whary MT, Fox JG. Helicobacter pylori-infected C57BL/6 mice with different gastrointestinal microbiota have contrasting gastric pathology, microbial and host immune responses. Sci Rep 2018; 8: 8014.
25. Velazquez EM, Nguyen H, Heasley KT, Saechao CH, Gil LM, Rogers AWL, Miller BM, Rolston MR, Lopez CA, Litvak Y, Liou MJ, Faber F, Bronner DN, Tiffany CR, Byndloss MX, Byndloss AJ, Baumler AJ. Endogenous Enterobacteriaceae underlie variation in susceptibility to Salmonella infection. Nat Microbiol 2019; 4: 1057-1064.
26. Sun JH, Li XL, Yin J, Li YH, Hou BX, Zhang Z. A screening method for gastric cancer by oral microbiome detection. Oncol Rep 2018; 39: 2217-2224.
27. Wu J, Xu S, Xiang C, Cao Q, Li Q, Huang J, Shi L, Zhang J, Zhan Z. Tongue Coating Microbiota Community and Risk Effect on Gastric Cancer. J Cancer 2018; 9: 4039-4048.
28. Cui J, Cui H, Yang M, Du S, Li J, Li Y, Liu L, Zhang X, Li S. Tongue coating microbiome as a potential biomarker for gastritis including precancerous cascade. Protein Cell 2019; 10: 496-509.
29. Youssef O, Lahti L, Kokkola A, Karla T, Tikkanen M, Ehsan H, Carpelan-Holmstrom M, Koskensalo S, Bohling T, Rautelin H, Puolakkainen P, Knuutila S, Sarhadi V. Stool Microbiota Composition Differs in Patients with Stomach, Colon, and Rectal Neoplasms. Dig Dis Sci 2018; 63: 2950-2958.
30. Qi YF, Sun JN, Ren LF, Cao XL, Dong JH, Tao K, Guan XM, Cui YN, Su W. Intestinal Microbiota Is Altered in Patients with Gastric Cancer from Shanxi Province, China. Dig Dis Sci 2019; 64: 1193-1203.
31. Gao JJ, Zhang Y, Gerhard M, Mejias-Luque R, Zhang L, Vieth M, Ma JL, Bajbouj M, Suchanek S, Liu WD, Ulm K, Quante M, Li ZX, Zhou T, Schmid R, Classen M, Li WQ, You WC, Pan KF. Association between gut microbiota and Helicobacter pylori-related gastric lesions in a high-risk population of gastric cancer. Front Cell Infect Microbiol 2018; 8: 202.

32. Iino C, Shimoyama T, Chinda D, Arai T, Chiba D, Nakaji S, Fukuda S. Infection of Helicobacter pylori and atrophic gastritis influence lactobacillus in gut microbiota in a Japanese Population. Front Immunol 2018; 9: 712.
33. Lloyd-Price J, Mahurkar A, Rahnavard G, Crabtree J, Orvis J, Hall AB, Brady A, Creasy HH, McCracken C, Giglio MG, McDonald D, Franzosa EA, Knight R, White O, Huttenhower C. Strains, functions and dynamics in the expanded Human Microbiome Project. Nature 2017; 550: 61-66.
34. Eren AM, Borisy GG, Huse SM, Mark Welch JL. Oligotyping analysis of the human oral microbiome. Proc Natl Acad Sci U S A 2014; 111: E2875-2884.
35. Chua EG, Chong JY, Lamichhane B, Webberley KM, Marshall BJ, Wise MJ, Tay CY. Gastric Helicobacter pylori infection perturbs human oral microbiota. PeerJ 2019; 7: e6336.
36. Mishiro T, Oka K, Kuroki Y, Takahashi M, Tatsumi K, Saitoh T, Tobita H, Ishimura N, Sato S, Ishihara S, Sekine J, Wada K, Kinoshita Y. Oral microbiome alterations of healthy volunteers with proton pump inhibitor. J Gastroenterol Hepatol 2018; 33: 1059-1066.
37. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT, Spector TD, Steves CJ. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016; 65: 749-756.
38. Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmsen HJ, Dijkstra G, Franke L, Xavier RJ, Jonkers D, Wijmenga C, Weersma RK, Zhernakova A. Proton pump inhibitors affect the gut microbiome. Gut 2016; 65: 740-748.

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