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EDITORIAL

Gastric microbiota and carcinogenesis - Current evidence and controversy

Growing research on the human microbiome, even beyond the gastrointestinal area, is not surprising mainly due to significant advances in study methods. Current reporting in this area is so intensive that clinicians are changing the unsuitable "bacterial flora" expression for more appropriate terms such as "microbiota" (the entire microbial community colonizing an ecologic niche), "microbiome" (their collective genome), or "dysbiosis" (microbial composition imbalance with respect to the normatively considered pattern) (1). Since the diseases involved in the altered microbiota hypothesis are increasing, its implication for cancer should come as no surprise to us.

Although limited data is available, microbiota changes could play a role in the susceptibility to certain types of tumors, especially gastric and colorectal neoplasia, by means of several mechanisms including dysbiosis-related inflammation and production of chemical carcinogens such as acetaldehyde and N-nitroso compounds (2,3). The systematic review about microbiota and gastric carcinogenesis, published by Dias-Jácome et al. in this issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* (4), illustrates the preliminary data about microbiota implications for cancer in human studies, as well as the controversy derived from these investigations. Gastric cancer is considered the model of bacteria-associated cancer due to its well-demonstrated association with *H. pylori* infection, so peculiarities related to the microbiota-*H. pylori* interaction enhance the enormous methodological complexity of this research (3).

The spreading of new gene sequencing methods (most of them based on 16S rRNA gene identification, present in all bacteria), and of complex bioinformatic methods for data processing, has led to several microbiome-related studies under specific conditions, as well as two main international projects for the study of human microbiome: the European MetaHIT, which offered the first gut microbiome catalogue (5), and the Human Microbiota Project in the United States, based on studies at different anatomical areas (6). In addition to taxonomic descriptions and a bacterial diversity study, these investigations focus on metabolic and functional microbiota properties (1). The interactions between gut microbiota and host, including poorly understood dysbiosis processes and their functional impact (i.e. on the local immune system by provoking inflammatory responses, barrier permeability (leading to bacterial translocation processes), or gut-brain axis interactions), constitute the basis of multiple basic and clinical hypotheses that implicate microbiota in several disorders, including, for example, irritable bowel syndrome (IBS) (7), inflammatory bowel disease (IBD) (8-10), hepatic cirrhosis (11,12), atopic disorders, metabolic syndrome, autism disorders (1), and cancer (2,3). However, with the probable exception of *Clostridium difficile* colitis (13), the current findings by these studies are preliminary and do not allow a pathogenic role of microbiota in these diseases to be established. In any case, further identification of biomarkers obtained from morphological and/or functional microbiome alterations, and their host interactions, could be of paramount significance should a pathogenic nexus be demonstrated, thus allowing the development of therapeutic interventions. Even as mere epiphenomena without causal pathogenic implications, these biomarkers could be useful diagnostic and/or prognostic tools.

The recent description of bacteria other than *H. pylori* in the stomach raised the hypothesis that *H. pylori* and microbiota interactions may be a relevant factor contributing to gastric carcinogenesis (which correlates, from a clinical point of view, for example, with MALT gastric lymphoma regression as observed in *H. pylori*-negative patients undergoing antibiotic therapy) (14). Gastric pH modifications induced by *H. pylori* may modify bacterial substrate availability and local immune responses, which may result in dysbiosis phenomena mediated, at least in part, by an *H. pylori*-microbiota interaction able to produce a pro-carcinogenic inflammatory response, for example, via the stimulation of toll-like receptors by bacterial products (15). In spite of other cancers implicated in microbiota disorders, as colorectal cancer (16), *H. pylori*-microbiota interactions raise complexity in the research of microbiota as related to gastric cancer.

As discussed in the paper by Dias-Jácome et al., concerns about small sample sizes and study designs are major limitations of this review. Discordant findings from human studies may be related to subject heterogeneity, different sample origins, and disparities in bacterial detection methods (partly due to the progressive replacement of traditional culture and genetic testing by newer sequencing methods). Also, gastric microbiome characterization is poorly understood when compared to other locations. Besides individual composition, the differentiation between permanent microbes and others passing from adjacent locations such as the oral cavity remains unclear. In any case, the findings of reviewed studies indicate a need for prospective studies including samples from different sites and an evaluation of time relationships between gastric microbiota, premalignant conditions, and

cancer, as well as a standardization of study methods (3). Nevertheless, designing translational and epidemiologic studies to assess potential factors in the host and epidemiologic environment represents the real challenge nowadays. The latter aspect is of great interest for gastric cancer considering its epidemiological characteristics. In spite of a reportedly decreased incidence over the last few decades, it remains the fifth cause of new cancer cases and the third cause of cancer-related mortality in 2012, with the highest incidence in Japan, China, Central and Eastern Europe, and Central and South America (17). A particular geographical distribution has been documented in many countries – for example, highest incidence areas in northern and northwestern Spain, which has persisted over the last decades concurrently with a decreasing incidence worldwide. Emphasis should be laid on the relevance of epidemiological factors as related to individual and environmental conditions, including dietary patterns and environmental exposures, in study designs, as has been the case in Spain (18). Presently, a recent study conducted in Colombia showed a different gastric microbiota composition between subjects from different gastric cancer incidence areas, independently of *H. pylori* status (19).

In summary, the systematic review of microbiota and gastric carcinogenesis published in this issue of *The Spanish Journal of Gastroenterology* (*Revista Española de Enfermedades Digestivas)* contributes to the preliminary evidence available on the complex role of gastric microbiota and its interaction with *H. pylori i*n gastric carcinogenesis. Research on this hypothesis is of great interest, since demonstrating a pathogenic implication of gastric microbiota may lead to identify diagnostic and/or prognostic biomarkers, as was recently reported for colorectal cancer (20). The underlying microbiota-related mechanisms of gastric carcinogenesis may be poorly understood until microbiological and epidemiological factors are incorporated into study designs, including factors related to the host and epidemiologic environment. Overcoming the excessive enthusiasm derived from interesting news in this area, an appropriate interpretation of study findings, and further corroboration in prospective studies, will improve the clinical management of diseases resulting from microbiome disorders, avoiding the potential problems of microbiota-related therapy in those clinical situations where its pathogenic contribution is uncertain and poorly understood (21,22).

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REFERENCES

1. Robles Alonso V, Guarner F. Linking the gut microbiota to human health. Br J Nutr 2013;109:S21-S26. DOI: 10.1017/S0007114512005235
2. Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer 2013;13(11):800-12. DOI: 10.1038/nrc3610
3. Vogtmann E, Goedert JJ. Epidemiologic studies of the human microbioma and cancer. Br J Cancer 2016;114:237-42. DOI: 10.1038/bjc.2015.465
4. Dias-Jácome E, Libânio D, Borges-Canha M, et al. Gastric microbiota and carcinogénesis: the role of non-Helicobacter pylori bacteria: A systematic review. Rev Esp Enferm Dig 2016;108(9):530-40.
5. Qin J, Li R, Raes J, et al. MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59-65. DOI: 10.1038/nature08821
6. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012;486:207-14. DOI: 10.1038/nature11234
7. Aguilera M, Cerdá-Cuéllar M, Martínez V. Antibiotic-induced dysbiosis alters host-bacterial interactions and leads to colonic sensory and motor changes in mice. Gut Microbes 2015;6(1):10-23. DOI: 10.4161/19490976.2014.990790
8. Gutiérrez A, Zapater P, Juanola O, et al. Gut bacterial DNA translocation is an independent risk factor of flare at short term in patients with Crohn´s disease. Am J Gastroenterol 2016;111(4):529-40. DOI: 10.1038/ajg.2016.8
9. Lopez-Siles M, Martinez-Medina M, Abella C, et al. Mucosa-associated Faecalibacterium prausnitzii phylotype richness is reduced in patients with inflammatory bowell disease. Appl Environ Microbiol 2015;81(21):7582-92. DOI: 10.1128/AEM.02006-15
10. Varela E, Marichanh C, Gallart M, et al. Colonisation by Faecalibacterium prausnitzii and maintenance of clinical remission in patients with ulcerative colitis. Aliment Pharmacol Ther 2013;38(2):151-61. DOI: 10.1111/apt.12365
11. Gómez-Hurtado I, Santacruz A, Peiró G, et al. Gut microbiota dysbiosis is associated with inflammation and bacterial translocation in mice with CCI4-induced fibrosis. PLoS One 2011;6(7):e23037. DOI: 10.1371/journal.pone.0023037
12. Santiago A, Pozuelo M, Poca M, et al. Alteration of the serum microbiome composition in cirrhotic patients with ascitis. Sci Rep 2016;6:25001. DOI: 10.1038/srep25001
13. Khanna S, Pardi DS, Kelly CR, et al. A novel microbiome therapeutic increases gut microbial diversity and prevents recurrent Clostridium difficile infection. J Infect Dis 2016;214(2):173-81. DOI: 10.1093/infdis/jiv766
14. Asano N, Iijima K, Koike T, et al. Helicobacter pylori-negative gastric mucosa-associated lymphoid tissue lymphomas: a review. World J Gastroenterol 2015;21(26):8014-20.
15. Pimentel-Nunes P, Goncalves N, Boal-Carvalho I, et al. Helicobacter pylori induces increased expression of Toll-like receptors and decreased Toll-interacting protein in gastric mucosa that persists throughout gastric carcinogenesis. Helicobacter 2013;18(1):22-32. DOI: 10.1111/hel.12008
16. Borges-Canha M, Portela-Cidade JP, Dinis-Ribeiro M, et al. Role of colonic microbiota in colorectal carcinogenesis: A systematic review. Rev Esp Enferm Dig 2015;107(11):659-71. DOI: 10.17235/reed.2015.3830/2015

17. Cao L, Yu J. Effect of Helicobacter pylori infection on the composition of gastric microbiota in the development of gastric cancer. Gastrointest Tumors 2015;2:14-25. DOI: 10.1159/000380893
18. Castaño-Vinyals G, Aragonés N, Pérez-Gómez B, et al. Population-based multicase-control study in commons tumors in Spain (MCC-Spain): rationale and study-design. Gac Sanit 2015;29(4):308-15. DOI: 10.1016/j.gaceta.2014.12.003
19. Yang I, Woltemate S, Piazuelo MB, et al. Different gastric microbiota compositions in two human populations with high and low gastric cancer risk in Colombia. Sci Rep 2016;6:18594. DOI: 10.1038/srep18594
20. Zackular JP, Rogers MAM, Ruffin IV MT, et al. The human gut microbiome as a screening tool for colorectal cancer. Cancer Prev Res (Phila) 2014;7(11):1112-21. DOI: 10.1158/1940-6207.CAPR-14-0129
21. Durchschein F, Petristsch W, Hammer HF. Diet therapy for inflammatory bowel diseases. World J Gastroenterol 2016;22(7):2179-94.
22. Ligaarden SC, Axelsson L, Naterstad K, et al. A candidate pro-biotic with unfavourable effects in subjects with irritable bowel syndrome: A randomized controlled trial. BMC Gastroenterol 2010;10:16 DOI: 10.1186/1471-230X-10-16