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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Mechanistic Understanding of the Symbiotic Relationship Between the Gut Microbiota and the Host

An Avenue Toward Therapeutic Applications

A new perspective of human body unravels an ecosystem that is established by a symbiotic relationship between the gut microbiota and the host. This interaction contributes to maintaining homeostasis in the host and provides a nutrient-rich environment for the microbiota.[1,2] The aberrant microbial composition and metabolic activity of the gut microbiome has been implicated as risk factors or a consequences of several diseases in humans, such as inflammatory bowel disease (IBD)[3,4] and colorectal cancer.[5] Therefore, precision modification of the gut microbiota is a potential approach for maintaining human health and for disease prevention and treatment.

There has been a growing interest in identification of the impact of vitamin D deficiency on carcinogenesis in cancer research. Vitamin D exerts its biologic functions through binding to the nuclear receptor, vitamin D receptor (VDR). Results from a large cohort suggest that higher level of VDR expression is associated with longer survival after surgical resection in patients with colorectal cancer.[6] This clinical evidence is supported by studies from Zhang et al[7] to elucidate a previously unrecognized mechanism through which the intestinal epithelial VDR regulates the homeostasis of the gut microbiome for preventing development of inflammation-associated colorectal cancer. Through a series of elegant *in vivo* and *in vitro* studies using human samples and mouse models of colorectal cancer, they report that the absence of VDR in intestinal epithelial cells results in shifting the gut bacterial profile toward that with high risk for colorectal cancer.[7] They further demonstrate that dysbiosis in mice with VDR deletion in intestinal epithelial cells promotes tumorigenesis through stimulating anti-inflammatory JAK/STAT3 signaling in intestinal epithelial cells.[7] It has been reported that alterations in the composition, distribution, or metabolism of the gut microbiota may produce an environment in the colon that promotes inflammation, dysplasia, and cancer.[8] Studies from Sun's group provide an encouraging base from which to further seek host factors that contribute to regulate the symbiotic relationship between gut microbial community and the host for maintaining intestinal homeostasis and protecting against diseases.

Although findings from previous studies have revealed that host genetics and environmental factors, such as diet, nutrient availability, immunologic responses, and disease states, shape the composition of the gut microbiota,[9,10] knowledge about how the host reinforces the microbial communities is not understood. Intestinal epithelial cells localizing on the mucosal surface exert front line responses to the gut microbiota and contribute to maintaining the intestinal homeostasis, thus these cells might have influence on the microbiota community in the gut. This speculation is supported by reported evidence that colonic epithelial cell-secreted extracellular vesicles participate in communicating with a probiotic bacterium, *Lactobacillus rhamnosus* GG, and promoting production of a functional factor by *L rhamnosus* GG for protecting intestinal epithelial cells against colitis.[11] Discovery from Sun's work identifies the involvement of VDR in intestinal epithelial cells in maintaining homeostasis of the gut microbiome.[7] Studies from the same group have revealed that VDR deletion in intestinal epithelial cells leads to abnormal Paneth cells and reduced antimicrobial peptides.[12] Thus, VDR-dependent antimicrobial peptide production in the intestinal tract may contribute to regulating the composition of the gut microbiota, and deficiency of VDR may induce the observed dysbiosis, leading to altered bacteria accumulated in tumors. This knowledge paves an avenue to investigating the feedback symbiosis between the host and the microbiome in the gut.

It should be noted that clinical progress of investigating JAK/STAT signaling in the pathogenesis of IBD, including Crohn's disease and ulcerative colitis, is promising, and JAK/STAT inhibitors are currently applied for treatment of patients with IBD.[13] Patients with IBD are at increased risk of colorectal cancer. Based on findings from Sun's group, JAK/STAT inhibitors could be potentially combined with VDR activators for treating chronic inflammation and preventing development of colitis-associated colorectal cancer. Verification of this preclinical observation in clinical trials will be indispensable in the future. Therefore, mechanistic understanding of the symbiotic relationship between the gut microbiota and the host could lay a foundation for investigating pathogenesis of diseases related to dysbiosis and for manipulating the gut microbiota as an approach for disease prevention and treatment.

FANG YAN, MD, PHD
Division of Gastroenterology, Hepatology & Nutrition
Department of Pediatrics
Vanderbilt University Medical Center
Nashville, Tennessee

References

1. Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486:207–214.

2. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Med 2016;8:51.
3. Frank DN, St Amand AL, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A 2007;104:13780–13785.
4. Haberman Y, Tickle TL, Dexheimer PJ, et al. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. J Clin Invest 2014;124:3617–3633.
5. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell Host Microbe 2014;15:317–328.
6. Vaughan-Shaw PG, Zgaga L, Ooi LY, et al. Low plasma vitamin D is associated with adverse colorectal cancer survival after surgical resection, independent of systemic inflammatory response. Gut 2020;69:103–111.
7. Zhang Y-G, Lu R, Wu S, Chatterjee I, Zhou D, Xia Y. Vitamin D receptor protects against dysbiosis and tumorigenesis via the JAK/STAT pathway in intestine. Cell Mol Gastroenterol Hepatol 2020;10:729–746.
8. Abreu MT, Peek RM Jr. Gastrointestinal malignancy and the microbiome. Gastroenterology 2014;146:1534–1546.
9. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nat Rev Microbiol 2016;14:20–32.
10. Spor A, Koren O, Ley R. Unravelling the effects of the environment and host genotype on the gut microbiome. Nat Rev Microbiol 2011;9:279–290.
11. Yang L, Higginbotham JN, Liu L, et al. Production of a functional factor, p40, by *Lactobacillus rhamnosus* GG is promoted by intestinal epithelial cell-secreted extracellular vesicles. Infect Immun 2019;87:e00113–e00119.
12. Wu S, Zhang YG, Lu R, et al. Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. Gut 2015;64:1082–1094.
13. Fernandez-Clotet A, Castro-Poceiro J, Panes J. JAK inhibition: the most promising agents in the IBD pipeline? Curr Pharm Des 2019;25:32–40.

Correspondence
Address correspondence to: Fang Yan, MD, PhD, 2215 Garland Avenue, MRB IV, Room 1035J, Nashville, Tennessee 37232. e-mail: fang.yan@vumc.org.

Conflicts of interest
The author discloses no conflicts.


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