EDITORIAL

Dysbiosis Associated With Esophageal Adenocarcinoma—A Novel Method to Detect Tissue-Associated Microbiome

Esophageal cancer (EC) is the eighth most common cancer diagnosed globally and one of the primary drivers of cancer-related deaths.[1] For the past half-century, the incidence of esophageal adenocarcinoma and its precursor, Barrett's esophagus, has been rapidly growing for reasons that are not properly explained by currently established risk factors. Gastroesophageal reflux disease, obesity, and the microbiome present in the upper gastrointestinal (GI) tract could contribute to the pathogenesis.[2] A recent study found patients with EC to have dysbiosis in the gut microbiome.[3] The GI microbiome has been shown to play an essential part in health,[4–6] in GI and other intestinal disorders,[7,8] as well as in several forms of cancer.[9,10] The distal esophagus contains a unique microbiome composed primarily of oral microbiota, which has been found to be altered in Barrett's esophagus and reflux esophagitis,[2] establishing the association of the microbiome with the pathophysiology of esophageal disorders. The role of the microbiome in esophageal disease progression as related to mucosal dysplasia is not well defined.

In this cross-sectional study,[11] the authors investigated the changes in the upper-GI-tract microbiome in the saliva, esophageal tissue, and feces in healthy patients as well as in patients with dysplasia, Barrett's esophagus, or esophageal adenocarcinoma using a novel method for characterizing the tissue-associated microbiome. They performed simultaneous integrated clinical-pathological and epidemiological correlations. Using the PAXgene fixation technique in conjunction with paraffin embedding of tissue biopsies for microbiome investigation, the authors demonstrated a unique microbial shift in tissue biopsies from esophageal adenocarcinoma patients compared to controls. However, total microbial diversity in salivary and fecal samples did not differ significantly across disease progression. The authors suggested that compared to saliva or the fecal microbiome, tissue-biopsy-linked microbiome has a tight association with esophageal adenocarcinoma. A key finding was the reduction in richness of species in esophageal adenocarcinoma compared to other phenotypes. suggesting a potential role of the mucosa-associated microbiome in the pathogenesis of esophageal adenocarcinoma. However, other studies[3] published recently have found 39 taxa that are more abundant in the feces of patients, with EC having a greater number of harmful bacteria that may be involved in the progression of carcinoma. Further analysis revealed, among other bacterium, that *Lachnospira* was found more abundantly in patients with EC and can possibly be used as a microbial biomarker and, possibly, direct treatment for EC.

The authors suggested that the mucosa-associated microbiome may interact directly with mucosal cells through surface proteins and metabolites. For example, *Fusobacterium nucleatum* has been shown to interact directly with mucosal cells in colon cancer to enhance colon cancer. This interaction involves binding to E-cadherin and also activation of toll-like receptor 4 (TLR-4) by lipopolysaccharides. A similar mechanism of TLR-4 activation may be involved in esophageal carcinogenesis. In a rat model of esophageal adenocarcinoma, upregulation of TLR 1–3, 6, 7, and 9 in cancerous tissue was noted compared to normal epithelium. The authors detected abundance of *Escherichia coli* in tumor tissues but not in the adjacent normal epithelium.[12]

This study highlights the differences in the mucosa-associated microbiome in esophageal adenocarcinoma. Methods to standardize mucosa-associated microbiome are described in the study and can provide a useful tool for investigators trying to understand the role of the gut microbiome in specific diseases.

Limitations of the study include the small number of samples analyzed and a potential confounder utilizing control patients with chronic gastritis. Larger studies are needed to see if assessing the microbiome in this fashion will have a role in clinical decision-making or risk assessment in the diagnosis and management of esophageal adenocarcinoma. Finally, and importantly, it remains to be determined if the dysbiosis is leading to the noted esophageal mucosal changes and subsequent adenocarcinoma or whether the abnormal mucosa favors the colonization of specific microbes. In other words, further study is needed to clarify a causal relationship. Further studies involving large cohorts of patients will need to be done to understand the contribution of the gut microbiome in the pathogenesis of esophageal adenocarcinoma. We acknowledge this article contributes to the excitement in the field.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136:E359–E386.
2. Snider EJ, Freedberg DE, Abrams JA. Potential role of the microbiome in Barrett's esophagus and esophageal adenocarcinoma. Dig Dis Sci 2016;61:2217–2225.
3. Deng Y, Tang D, Hou P, et al. Dysbiosis of gut microbiota in patients with esophageal cancer. Microb Pathog 2021; 150:104709.

4. Nejad MR, Ishaq S, Al Dulaimi D, et al. The role of infectious mediators and gut microbiome in the pathogenesis of celiac disease. Arch Iran Med 2015;18:244–249.
5. Ohkusa T, Okayasu I, Ogihara T, et al. Induction of experimental ulcerative colitis by Fusobacterium varium isolated from colonic mucosa of patients with ulcerative colitis. Gut 2003;52:79–83.
6. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology 2014;146:1489–1499.
7. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860–867.
8. Fujimura KE, Lynch SV. Microbiota in allergy and asthma and the emerging relationship with the gut microbiome. Cell Host Microbe 2015;17:592–602.
9. Vogtmann E, Goedert JJ. Epidemiologic studies of the human microbiome and cancer. Br J Cancer 2016;114:237–242.
10. Garrett WS. Cancer and the microbiota. Science 2015;348:80–86.
11. Radani N, Metwaly A, Reitmeier S, et al. Analysis of fecal, salivary and tissue microbiome in Barrett esophagus, dysplasia and esophageal adenocarcinoma. Gastro Hep Adv 2022;1:755–766.
12. Zaidi AH, Kelly LA, Kreft RE, et al. Associations of microbiota and toll-like receptor signaling pathway in esophageal adenocarcinoma. BMC Cancer 2016;16:52.

Received May 24, 2022. Accepted May 24, 2022.

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Conflicts of Interest:
The authors disclose no conflicts. Shanthi Srinivasan is a member of the Board of Editors. Their paper was handled in accordance with our conflict-of-interest policy. See https://www.ghadvances.org/content/authorinfo#conflict_of_interest_policy for full details.

Funding:
This work is supported by U.S. National Institutes of Health (NIH) grants R01DK080684 and R01DK044234 and VA Research and Development Merit Review Award I01BX000136-08.

Ethical Statement:
This commentary did not require the approval of an institutional review board.

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2772-5723
https://doi.org/10.1016/j.gastha.2022.05.016