Received: 1 March 2017 | Accepted: 22 April 2017

DOI: 10.1002/ags3.12014

REVIEW ARTICLE

WILEY AGS Annals of Gastroenterological Surgery Open Access

Review of the gut microbiome and esophageal cancer: Pathogenesis and potential clinical implications

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Abstract

Esophageal cancer ranks among the most aggressive malignant diseases. The limited improvements in treatment outcomes provided by conventional therapies have prompted us to seek innovative strategies for treating this cancer. More than 100 trillion microorganisms inhabit the human intestinal tract and play a crucial role in health and disease conditions, including cancer. The human intestinal microbiome is thought to influence tumor development and progression in the gastrointestinal tract by various mechanisms. For example, *Fusobacterium nucleatum*, which primarily inhabits the oral cavity and causes periodontal disease, might contribute to aggressive tumor behavior through activation of chemokines such as CCL20 in esophageal cancer tissue. Composition of the intestinal microbiota is influenced by diet, lifestyle, antibiotics, and pro- and prebiotics. Therefore, by better understanding how the bacterial microbiota contributes to esophageal carcinogenesis, we might develop novel cancer prevention and treatment strategies through targeting the gastrointestinal microflora. This review discusses the current knowledge, available data and information on the relationship of microbiota with esophagitis, Barrett's esophagus, esophageal adenocarcinoma and squamous cell carcinoma.

KEYWORDS
esophagus, microbiome, microbiota

1 | INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related death and the eighth most commonly diagnosed cancer worldwide.[1] The predominant histological types of esophageal cancer are adenocarcinoma and squamous cell carcinoma.[2] Adenocarcinoma of the distal esophagus predominates in the West, whereas squamous cell carcinoma, which tends to localize in the middle thoracic esophagus, predominates in the East. Molecular features also differ between adenocarcinoma and squamous cell carcinoma; for example, squamous cell carcinomas showed frequent genomic amplifications of *CCND1* and *SOX2* and/or *TP63*, whereas *ERBB2*, *VEGFA* and *GATA4* and *GATA6* were more commonly amplified in adenocarcinomas.[3] Traditionally, both adenocarcinomas and squamous cell tumors have been treated by surgical resection.[4] However, despite the development of multimodal therapies including surgery, chemotherapy, radiotherapy, and chemoradiotherapy, the prognosis remains poor even in patients who have undergone complete resection.[5] Therefore, further studies are needed to clarify the pathogenesis of esophageal cancer and to explore new diagnostic and therapeutic possibilities.

Microbiome research is a rapidly advancing field in human cancers.[6–10] More than 100 trillion bacteria inhabit the human body

and form their own flora (ie microbiomes) in individual organs. The gut microbiota appears haphazard in infants, but begins resembling the adult microbiome by age 3 years. Nevertheless, the microbial distribution from the esophagus to the rectum varies spatially and temporally throughout the individual's lifespan. The normal gut microbiota carries out specific functions in host nutrient metabolism, xenobiotic and drug metabolism, structural integrity maintenance of the gut mucosal barrier, immunomodulation, and protection against pathogens.[11–15] Recently, the gut microbiome has been shown to play a crucial role in health, as well as in diseases such as obesity,[16] inflammatory bowel disease,[17,18] diabetes,[19,20] non-alcoholic fatty liver disease,[21–23] and several types of cancers.[24,25] Experimental evidence indicates that the human intestinal microbiome can influence tumor development and progression in the gastrointestinal tract by damaging DNA, activating oncogenic signaling pathways, producing tumor-promoting metabolites, and suppressing the antitumor immune response.[7,25–29] As the gastrointestinal microbiota can be modified through the rational deployment of antibiotics, probiotics, and prebiotics,[30–32] a better understanding of the relationship between human cancer and the microbiome may have clinical implications.

The present review discusses current knowledge on the relationship between the microbiome and esophageal cancer. Importantly, because two histological types (adenocarcinoma and squamous cell carcinoma) present as different diseases in terms of their epidemiology, pathogenesis, and tumor biology, the role of the microbiome is discussed separately for each histological type.

2 | MICROBIOME OF THE NORMAL ESOPHAGUS

Distribution of the gut microbiota varies temporally and spatially at the genus level and higher. From the oral cavity, through the esophagus and distally to the rectum, the diversity and number of bacteria changes markedly, ranging from 10^1 per gram of contents in the esophagus and stomach to 10^{12} per gram of contents in the colon and distal gut.[33] Importantly, the esophagus, unlike other luminal organs of the digestive system, does not retain food contents.

In the 1990s, microbiological studies depended mainly on conventional bacterial culture-based methods. These studies demonstrated that the esophagus is either sterile or contains only a few transient microbes swallowed from the oropharynx or ejected from the stomach by gastroesophageal reflux.[34] Gagliardi et al.[34] revealed that *Streptococcus viridans* is the most frequent microorganism in both the normal esophagus and the oropharynx. These findings were consolidated by Norder Grusell et al.,[35] who collected brush samples and biopsy samples from the esophagus, and reported the occurrence rate of *Streptococcus viridans* as 95-98%. These studies support a possible correlation between the flora in the oropharynx and the esophagus. However, as most of the autochthonic esophageal microbiome is viable but non-culturable, it will likely be missed by standard culturing methods. More recently, the diversity of the non-culturable microbiota has been characterized by advanced approaches such as polymerase chain reaction (PCR) of 16S ribosomal RNA.[36] Pei et al.[37] examined the normal esophagus by broad-range 16S rDNA PCR and identified 95 species in six phyla: Firmicutes (eg *Streptococcus*), Bacteroides (eg *Prevotella*), Actinobacteria (eg *Rothia*), Proteobacteria (eg *Haemophilus*), Fusobacteria (eg *Fusobacterium*), and TM7. Remarkably, the findings were similar across specimens, suggesting a stable esophageal biota that is distinct from the flora of the oropharynx, stomach, and food bolus in transit. Microscopic examination of the tissue confirmed a close association between the bacteria and the cell surfaces of the mucosal epithelium in situ, suggesting a residential, rather than a transient, biota.

Collectively, the normal esophagus has a distinct microbiome of predominantly oral flora. Members of the phylum Firmicutes as represented by *Streptococcus viridans* appear to be major components of the microbiota of the normal esophagus, although the presence of several other phyla (eg Bacteroides, Actinobacteria, Proteobacteria, Fusobacteria, TM7) has also been reported.

3 | MICROBIOME IN ESOPHAGITIS AND BARRETT'S ESOPHAGUS

Gastroesophageal reflux disease (GERD) is an important risk factor for esophageal adenocarcinoma. GERD can lead to erosive esophagitis and (after an aberrant healing process) to a metaplastic, specialized intestinal epithelium (ie Barrett's esophagus).[38] Among the 6-14% of GERD patients who develop Barrett's esophagus, 0.5-1% will progress to adenocarcinoma.[39] In a meta-analysis of population-based studies, weekly symptoms of GERD were estimated to increase the risk of esophageal adenocarcinoma approximately fivefold.[40]

Several studies have documented microbiome status in esophagitis and Barrett's esophagus. In a microscopic study of Barret's esophageal biopsy specimens, Osias et al.[41] found that cultivable bacteria were closely associated with the mucosa of the specimens. They concluded that Barrett's mucosa are colonized rather than transiently visited by resident bacteria. Macfarlane et al.[42] isolated a broader range of bacteria from patients with Barrett's esophagus than from individuals without Barrett's esophagus, suggesting a higher microbiological diversity in patients with Barrett's esophagus. Using 16S rDNA sequencing technology, Yang et al.[43] characterized the diversity of the distal esophagus microbiota in individuals with normal esophagus, reflux esophagitis and Barrett's esophagus. They classified the esophageal microbiota into two types (Figure 1). Type I microbiome, mainly associated with normal esophagus, was predominated by Gram-positive bacteria, primarily phylum Firmicutes. Type II microbiome contained a greater proportion of Gram-negative anaerobes/microaerophiles (phyla Bacteroidetes, Proteobacteria, Fusobacteria, and Spirochaetes), and was primarily correlated with reflux esophagitis and Barrett's esophagus. As the microbiomes did not differ between GERD and Barrett's esophagus patients, the authors concluded that inflammation and intestinal metaplasia are associated with global alteration of the microbiome in the distal esophagus.

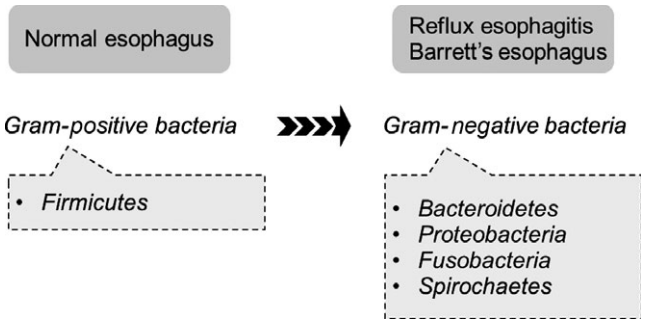

FIGURE 1 Microbiome status of normal esophagus, reflux esophagitis, and Barrett's esophagus. In the human distal esophagus, inflammation and intestinal metaplasia are associated with global alteration of the microbiome[43]

Using culture-independent techniques, Liu et al.[44] examined the bacterial composition at the 16S rDNA gene site in subjects with a normal esophagus, reflux esophagitis, or Barrett's esophagus. *Veillonella*, *Prevotella*, *Neisseria*, and *Fusobacterium* prevailed in patients with reflux esophagitis and Barrett's esophagus, but were not detected in normal esophagus. More recently, Gall et al.[45] showed that *Streptococcus* and *Prevotella* dominate the esophageal microbiota of Barrett's esophagus patients, with no substantial intraindividual differences between normal and metaplastic esophageal mucosa. They also found a significant association between the *Streptococcus/Prevotella* ratio and some important risk factors for Barrett's esophagus and esophageal adenocarcinoma (eg waist-to-hip ratio, hiatal hernia length). Overall, the esophageal bacteria differ among normal esophagus, reflux esophagitis and Barrett's esophagus, supporting that esophageal disease is related to the bacterial community profile, possibly through the innate immune system. Gram-negative organisms, which predominate in reflux esophagitis and Barrett's esophagus, produce specific constituents such as lipopolysaccharide (LPS) that activate the innate immune responses.[46] Either directly or indirectly, LPS may stimulate the innate immune system's Toll-like receptor (TLR) 4 in the epithelial or inflammatory cells, leading to nuclear factor kappa B (NF-κB) activation. Increased NF-κB activation is associated with elevated levels of inflammatory cytokines.[47] Activation of the NF-κB pathway increases stepwise along the spectrum of reflux esophagitis, Barrett epithelium, and adenocarcinoma, paralleling the increases in interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α.[48–50] Taken together, in reflux esophagitis and Barrett's esophagus, the change of microbiomes (ie increased Gram-negative organisms) may contribute to esophageal adenocarcinoma by inducing chronic inflammation, triggering a cascade that leads to adenocarcinoma.[46]

4 | MICROBIOME AND ESOPHAGEAL ADENOCARCINOMA

Given the important role of the gut microbiome in human malignancies, a better understanding of the microbiome in esophageal cancer is increasingly important. In the 1980s, culture-based methods and surgically resected specimens of esophageal adenocarcinoma and squamous cell carcinoma revealed the same microbiota in normal and cancerous tissues. However, these studies were focused on identifying pathogens related to postoperative infections, rather than comparing the non-pathogenic bacteria in esophageal cancer cases and control cases.[51–53] More recently, Narikiyo et al.[54] characterized the microbiota of normal and cancerous esophageal tissue by 16S sequencing technology. Cancerous tissues were obtained from 20 patients undergoing surgical resection for esophageal cancer. Both microbiota were consistently dominated by the oral periodontopathic spirochete *Treponema denticola*, *Streptococcus mitis*, and *Streptococcus anginosus*, but the pathological subtypes of the tumors were not specified.[54] Using a mixed culture-dependent and culture-independent approach, Blackett et al.[55] compared the microbiota in reflux-asymptomatic controls and in patients with GERD, Barrett's esophagus, and esophageal adenocarcinoma. *Campylobacter* were significantly more enriched in GERD and Barrett's esophagus than in the controls and esophageal adenocarcinoma. In addition, cytokines associated with carcinogenesis (eg IL-18) were more highly expressed in the tissues colonized by *Campylobacter*.[55] Given the potential human pathogenicity of *Campylobacter* species (which has been recently recognized),[56] the role of *Campylobacter* in esophageal adenocarcinoma progression might mimic that of *Helicobacter pylori* in gastric cancer.

The relationship between the microbiome and esophageal adenocarcinoma development has been experimentally investigated. Sawada et al.[57] investigated whether altering the microbiome with antibiotics affected the development of esophageal adenocarcinoma in a rat model with esophagojejunostomy. Terminal restriction fragment length polymorphism analysis showed that the esophageal microbiomes differed between the two groups; for instance, the proportions of *Lactobacillales* and *Clostridium* were reduced and elevated in the antibiotics group, respectively. However, the altered microbiome did not affect the incidence of esophageal adenocarcinoma. In a rat model with esophagojejunal anastomosis, Zaidi et al.[58] revealed a prevalence of *Escherichia coli* in Barrett's esophagus and esophageal adenocarcinoma; moreover, TLR 1-3, 6, 7 and 9 were significantly upregulated in esophageal adenocarcinoma compared with normal epithelium. This suggests an association between the TLR signaling pathway and *E. coli*, hinting that early molecular changes are mediated by microbes in the rat model of esophageal adenocarcinoma carcinogenesis.[58] At this time, less conclusive information is available about the effects of the microbiome on esophageal adenocarcinoma. Nonetheless, alteration of microbiome status is potentially involved in the progression of GERD and Barrett's esophagus toward adenocarcinoma.

5 | MICROBIOME AND ESOPHAGEAL SQUAMOUS CELL CARCINOMA

The microbiome is less well characterized in esophageal squamous cell carcinoma than in esophageal adenocarcinoma.[59] Yu et al.[60]

observed a negative correlation between esophageal microbial richness and esophageal squamous dysplasia (the precursor lesion of esophageal squamous cell carcinoma) in a human oral microbe identification microarray. They suggested that individuals with lower esophageal microbial complexity are more prone to developing esophageal squamous dysplasia.[60] Another study using 16S rDNA sequencing technology demonstrated that, relative to controls, the gastric corpus microbiota of patients affected by esophageal squamous dysplasia and esophageal squamous cell carcinoma are enriched in Clostridiales and Erysipelotrichales, suggesting that gastric dysbiosis is involved in the progression from esophageal squamous dysplasia to squamous cell carcinoma.[61] Gao et al.[62] revealed that a specific microbiome *Porphyromonas gingivalis* infects the cancerous and adjacent esophageal mucosa of esophageal squamous cell carcinoma patients but not the healthy mucosa of controls, supporting a pathogenesis role of this organism in esophageal squamous cell carcinoma. The presence of *Porphyromonas gingivalis* was also positively correlated with the severity (ie cancer cell differentiation and metastasis) of esophageal squamous cell carcinoma and with poor clinical outcome. Therefore, *Porphyromonas gingivalis* may serve as a biomarker of esophageal squamous cell carcinoma. According to Chen et al.,[63] altered bacterial microbiota in the saliva is related to a higher risk of esophageal squamous cell carcinoma. The carriage of genera Lautropia, Bulleidia, Catonella, Corynebacterium, Moryella, Peptococcus and Cardiobacterium is lower in esophageal squamous cell carcinoma patients than in individuals without this cancer.

Given that poor oral health increases the risk of esophageal squamous cell carcinoma,[64] these findings should be verified in prospective and long-term cohort studies, along with functional studies. By establishing the association between the oral microbiome and risk of esophageal squamous cell carcinoma, we can better understand cancer etiology, and possibly develop a novel research paradigm for cancer chemoprevention.

Recently, we revealed that the prognosis of esophageal squamous cell carcinoma relates to the presence of *Fusobacterium nucleatum*, which primarily inhabits the oral cavity and causes periodontal disease.[65] *Fusobacterium nucleatum* is frequently detected in colon cancer tissue, and may influence the development of colorectal cancer. Given the close proximity of the esophagus to the oral cavity, we suspect that *Fusobacterium nucleatum* also plays an important role in esophageal cancer. Using real-time PCR analysis, we assessed DNA in the cancer tissues of 325 patients who underwent surgical removal of esophageal cancer. Seventy-four out of 325 patients (nearly 23%) contained *Fusobacterium nucleatum* in their cancer tissues. Importantly, the presence of *Fusobacterium nucleatum* in cancer tissue was associated with significantly shorter survival time. Using microarray data, we also identified significant pathways in *Fusobacterium nucleatum*-positive esophageal cancer tissues. The top-ranked KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway in *Fusobacterium nucleatum*-positive tissues was "Cytokine-cytokine receptor interaction". Detailed analysis of these data revealed that the genes of specific chemokines (ie CCL20) had increased in number, suggesting that *Fusobacterium nucleatum* contributes to the acquisition of aggressive tumor behavior by activating chemokines such as CCL20. Further analysis by more institutions, preferably worldwide, is desired because intestinal flora differ among individuals. Accumulating evidence suggests the crucial role of gut microbiota in the development and progression of esophageal squamous cell carcinoma. Further studies are needed to validate the previous findings and to elucidate the mechanism(s) whereby the gut microbiome affects tumor behavior.

6 | FUTURE DIRECTIONS

By elucidating the mechanisms and microbiome contributions to the development and progression of esophageal cancer, we hope to develop novel therapeutics and strategies that treat or prevent esophageal cancer by modulating the microbiota (Figure 2). First, importantly, the composition of intestinal microbiota can be modified by antibiotics, probiotics, prebiotics or microbiota transplants. Limited-spectrum and non-absorbable antibiotics can remove or suppress unwanted components of the human microbiome. Probiotics can introduce missing microbial components with known beneficial functions for the human host. Prebiotics can maximize sustainable changes in the human microbiome by enhancing the proliferation of beneficial microbes or probiotics. Prebiotics or probiotics might target the microbiome for cancer prevention, especially in high-risk populations. Second, the microbiota's potential ability to modulate the toxicity and efficacy of chemotherapy has also attracted interest.[66] For example, the microbiota and immune system have reportedly enhanced the efficacy of oxaliplatin, a platinum-based anticancer drug that treats esophageal cancer.[67] Gut microbiota stimulate the production of reactive oxygen species (ROS) by immune cells. ROS enhance the DNA damage caused by oxaliplatin, blocking DNA replication and transcription and resulting in cell death.[67] Third, given the intertwined nature of the microbiota and the immune system, microbiota likely influence their host's responsiveness to immunotherapy. Immunotherapy (eg antibodies to PD-L1) ranks among the most exciting and successful developments in

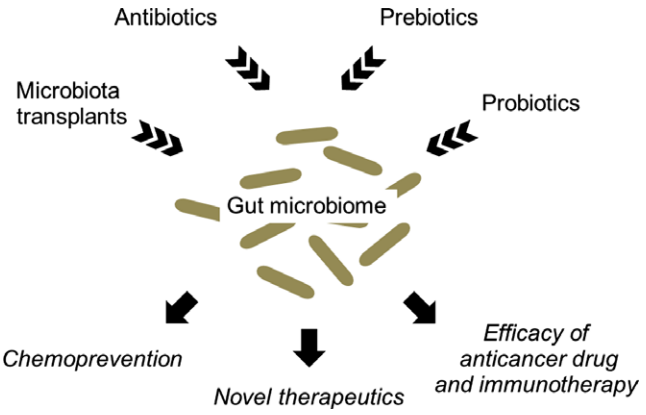

FIGURE 2 Clinical implication of the gut microbiome in human cancers

cancer care over the past decade. Antibiotic-mediated disruption of the microbiota impaired the effectiveness of CpG oligonucleotide immunotherapy in mice with subcutaneous tumors.[25,67] Fourth, the microbiota is a potential biomarker of diagnosis or clinical outcome. If correct, the relationship between *Fusobacterium nucleatum* and poor clinical outcome identified in our previous work will have clinical implications.[65]

7 | CONCLUSIONS

Accumulating evidence suggests that imbalanced gut microbiota induces changes in the enteric environment that lead to esophageal mucosal inflammation or tumorigenesis. Understanding the diverse ways that the bacterial microbiota contributes to esophageal carcinogenesis will open new possibilities for the diagnosis, prevention and treatment of esophageal cancer.

DISCLOSURE

Conflict of Interest: Authors declare no conflicts of interest for this article.

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How to cite this article: Baba Y, Iwatsuki M, Yoshida N, Watanabe M, Baba H. Review of the gut microbiome and esophageal cancer: Pathogenesis and potential clinical implications. *Ann Gastroenterol Surg*. 2017;1:99–104. https://doi.org/10.1002/ags3.12014