Microbiome, Innate Immunity, and Esophageal Adenocarcinoma

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KEYWORDS

• Reflux • Barrett esophagus • Adenocarcinoma • Microbiome
• Chronic inflammation • Viruses • Bacteria • Innate immunity

KEY POINTS

- With the development of culture-independent technique, a complex microbiome has been established and described in the distal esophagus.
- Over recent decades, the incidence of esophageal adenocarcinoma (EAC), a relatively rare cancer with high mortality, has increased dramatically in the United States.
- Several studies documenting an altered microbiome associated with EAC and its precedents (ie, Barrett esophagus and reflux esophagitis) suggest that dysbiosis may be contributing to carcinogenesis, potentially mediated by interactions with toll-like receptors.
- Investigations attempting to associate viruses, in particular human papilloma virus, with EAC have not been as consistent. Regardless, currently available data are cross-sectional and therefore cannot prove causal relationships.
- Prospectively, microbiome studies open a new avenue to the understanding of the etiology and pathogenesis of reflux disorders and EAC.

INTRODUCTION

Esophageal adenocarcinoma (EAC) is a relatively rare but aggressive cancer that has been increasing in incidence, particularly among white men.[1–3] EAC typically develops in the distal esophagus in response to mucosal injury, such as with exposure to gastric

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reflux, and is preceded by Barrett esophagus (BE), a form of epithelial metaplasia. Beyond demographics, the major risk factors for EAC are gastroesophageal reflux disease (GERD), cigarette smoking, obesity, and low fruit and vegetable consumption. At a single cancer center, these risk factors represented a combined population-attributable risk of nearly 80%.[4]

The relationship between GERD and EAC is complex. Symptomatic GERD is a strong risk factor for EAC,[5,6] with increasing odds of an association as symptoms manifest for a longer duration or with increased frequency.[7] However, esophagitis may develop in patients without significant acid exposure.[8] The complications of GERD (esophagitis,[9] BE,[10] and EAC[4]) likewise may arise in the absence of preceding symptoms. Thus, acid reflux alone may not fully account for the pathogenesis of EAC. We hypothesize that characteristics of the esophageal microbiome facilitate the development of disease.

MICROBIOME OF THE NORMAL ESOPHAGUS

Early work to characterize an esophageal microbiome was undertaken by surgeons in the hope of preventing infections after thoracotomy.[11–14] These studies used conventional bacterial culture and therefore missed most of the indigenous esophageal biota, which is in a viable but nonculturable state.[15,16] More recent approaches to characterize complex microbial communities have used polymerase chain reaction (PCR) of 16S ribosomal RNA[17] to better characterize nonculturable bacteria.

Using culture-independent technique to examine biopsies of normal esophagus, Pei and colleagues[18] first described a complex bacterial biota in the distal esophagus. Ninety-five species were identified, including members of 6 phyla: Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Fusobacteria, and TM7. Two phyla seen in the oral cavity, Spirochaetes and Deferribacteres, were not present. Remarkably, findings were similar across specimens, suggesting a stable esophageal biota that is distinct from the flora of the oropharynx, stomach, or food bolus in transit. Microscopic examination of the tissue confirmed a close association of the bacteria with the cell surfaces of the mucosal epithelium in situ, suggesting a residential, rather than a transient, biota.

MICROBIOME IN DISEASE STATES

In 2005, Pei and colleagues[19] undertook the first study to apply cultivation-independent technique to the microbiome in esophageal disease, with the goal of demonstrating feasibility. Two 16S rRNA gene clones were recovered and examined from each of the esophageal biopsies taken from 24 subjects (9 with normal mucosa, 12 with GERD, and 3 with BE). As expected, bacterial signals were successfully detected in all biopsies, and the overall diversity and community membership resembled those of the normal esophageal microbiome.

A more comprehensive approach was taken by Yang and colleagues[20] in 2009. Representing one of the largest human microbiome studies to date, a total of 6800 16S rRNA gene clones from 34 subjects were analyzed by Sanger sequencing. Using both unsupervised and phenotype-guided clustering analyses, samples were found to contain 1 of 2 distinct microbiomes. Microbiome type I was mainly associated with normal esophagus and was predominated by gram-positive bacteria from the Firmicutes phylum, of which *Streptococcus* was the most dominant genus. Microbiome type II had greater proportion of gram-negative anaerobes/microaerophiles (phyla Bacteroidetes, Proteobacteria, Fusobacteria, and Spirochaetes) and primarily correlated with reflux esophagitis (RE) (odds ratio, 15.4) and BE (odds ratio, 16.5). The microbiome did not differ between patients with GERD and patients with BE.