The Gastric Microbiome and Its Influence on Gastric Carcinogenesis

Current Knowledge and Ongoing Research

Chao Zhang, PhD[a,b], Sarah Ellen Powell, PhD[b], Doron Betel, PhD[a,b], Manish A. Shah, MD[b,c,*]

KEYWORDS

• Gastric microbiome • *Helicobacter pylori* • EBV • Gastric cancer
• Microbial identification

KEY POINTS

- Gastric cancer is the fourth leading cause of cancer-related deaths worldwide, most commonly caused by chronic infection with intracellular bacterium *Helicobacter pylori.*
- *H pylori* is the most common cause of peptic ulcer disease. The drivers that determine malignant transformation over self-limiting ulcer and chronic gastritis remain unknown.
- In addition to *H pylori*, the stomach hosts a diverse and active microbial community whose role in host response and pathogenesis has yet to be fully delineated.
- The gastric microbiome is likely a marker of host health and influences the inflammatory response within upper gastrointestinal cancers.

INTRODUCTION

The human body is thought to house more than 100 trillion microbes. These microbial communities have a significant impact on their human hosts.[1] They influence everything from pathogen defense to digestion to immune system maturation. The microbiome is also linked to the development of several autoimmune diseases and cancers, including colorectal, pancreatic, and gastric cancers.[2] A major risk factor for the development of gastric cancer (GC) is infection by the bacteria *Helicobacter*

[a] Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY 10021, USA; [b] Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medicine, New York, NY 10021, USA; [c] Gastrointestinal Oncology Program, Center for Advanced Digestive Care, Sandra and Edward Meyer Cancer Center, New York-Presbyterian Hospital, Weill Cornell Medicine, New York, NY 10021, USA
* Corresponding author. Division of Hematology and Medical Oncology, New York-Presbyterian Hospital, Weill Cornell Medicine, 1305 York Avenue, Room Y1247, New York, NY 10021.
E-mail address: mas9313@med.cornell.edu

Hematol Oncol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.hoc.2017.01.002 **hemonc.theclinics.com**

pylori, a common inhabitant (although not always pathogen) of the human stomach. GC is the fourth most common cancer worldwide. The study of *H pylori* and its associated gastric microbiome is of increasing importance in the study of gastrointestinal (GI) diseases and chronic immune response. Understanding the impact of microbial community structure and function on tumorigenesis and immune response will broaden the understanding of GC tumorigenesis and may impact development of therapeutic and preventative approaches.

MICROBIOME DIVERSITY ALONG THE GASTROINTESTINAL TRACT

Although parts of the GI tract are arguably primed for microbial life, the stomach is not intuitively such an environment. The human stomach is particularly unique in that its inhabitants are challenged by several antimicrobial chemicals, enzymes, structural barriers, and highly acidic conditions that are not collectively present in any other part of the human body. Although transient microbes may temporarily survive such an environment through spore formation, thickened cell walls, and acid resistance, those colonizing this environment must adapt to a highly variable and ever-changing landscape.

A benefit of the harsh gastric environment is that it enables segregation of digestive absorption of food from most of the microbial biomass, thereby prioritizing nutrient absorption. The production of salivary enzymes such as lipase and amylase as well as the conversion of nitrates into the antimicrobial compound NO_2 by *Lactobacilli* in the mouth begins the process of dramatically reducing the microbial biomass before microbial entry into the stomach.[3] Microbes entering the stomach are then exposed to hydrochloric acid secreted by parietal cells, which then enables the conversion of pepsinogen into pepsin, a potent enzyme that denatures proteins and inhibits microbial survival and growth.

In addition to antimicrobial enzymes, there are several other mechanisms used by the host to prevent microbial proliferation within the stomach. Antimicrobial mechanisms include the expression of immunoglobulin A (IgA), which is thought to limit mucosal penetration and potentially shape diversity of normal gut flora.[4] In addition, the constitutive production of defensins and cathelicidins in epithelial cells as well as triggered expression of C-type lectins help to protect host mucosa from over colonization.[5]

These challenges largely explain the discordance in the bacterial density in the stomach as compared with the colon. By some estimates, microbial cell numbers increase from 10^1 to 10^3 colony-forming units (CFU) mL^{-1} in the stomach to 10^{11}–10^{12} cfu mL^{-1} in the large intestine. Notably, the colonic bacterial density exceeds that found in any other known ecosystem.[5,6]

Gastric Bacteria

Bacteria that are able to reside in the stomach demonstrate several mechanisms that enable colonization within the harsh gastric environment. Acid resistance is a significant factor for bacterial survival and proliferation. Bacteria such as *Escherichia coli* and *H pylori* exhibit increased membrane protein production and buffering capacity, allowing these bacteria to resist acid degradation upon entry to the stomach. Subsequent structural, enzymatic, and adhesive adaptive advantages further enable these bacteria and others to colonize the environment.[7,8]

Multiple studies have attempted to characterize the microbial components of the stomach, either directly from biopsy samples or from gastric juices. There is increasing evidence that the microbiome profiles of the human stomach vary widely between