The Interrelationships of the Gut Microbiome and Inflammation in Colorectal Carcinogenesis

Margaret Cho, MD[a], Janell Carter, MD[a], Saul Harari, MD[a], Zhiheng Pei, MD, PhD, FASCP[a,b,c,*]

KEYWORDS

• Gut microbiome • Colorectal cancer • Inflammation • Carcinogenesis

KEY POINTS

- The cause of colorectal cancer (CRC) is multifactorial with genetic, molecular, inflammatory, and environmental risk factors. Recently, the gut microbiota has been recognized as a new environmental contributor to CRC in both animal models and human studies.
- An additional interplay of the gut microbiome with inflammation is also evident in studies that have shown that inflammation alone or the presence of bacteria/bacterial metabolites alone is not enough to promote tumorigenesis.
- Complex interrelationships with the gut microbiome, inflammation, genetics, and other environmental factors are evident in progression of colorectal tumors.

INTRODUCTION

The last decade has brought a revolution in the understanding of microorganisms vis-à-vis their environment/mammalian hosts. These radical changes in thought not only challenge ideas that dominated biological and medical sciences for more than a hundred years but at a visceral level call, into question the definition of the human identity. The emergence of the germ theory of disease in the late nineteenth century,

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[a] Department of Pathology, New York University School of Medicine, 560 First Avenue, New York, NY 10016, USA; [b] Department of Medicine, New York University School of Medicine, 560 First Avenue, New York, NY 10016, USA; [c] Department of Veterans Affairs New York Harbor Healthcare System, 423 East 23rd Street, Room 6030W, New York, NY 10010, USA
* Corresponding author. Veterans Affairs Medical Center, 423 East 23rd Street, Room 6030W, New York, NY 10010.
E-mail address: zhiheng.pei@med.nyu.edu

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highlighted by the propagation of Robert Koch's famous postulates, and the ensuing discovery of antibiotics some decades later, exemplify the view of microorganism as a foreign other, with disease-causing potential (pathogens) that often needs to be treated via medical eradication. In the common parlance, germs are bad and not to be spread. Although there was a movement recognizing the potential for bacteria to benefit their host (probiotics) during the twentieth century, it is only in the last decade or so that the true extent, complexity, and intimacy of this relationship have taken form.

It is now generally accepted that bacteria are (critical to their ecosystems) ubiquitous and colonizers of all exposed human body surfaces, including the entire alimentary tract. Bacterial organisms living in/on a human host outnumber that host's native cells by a factor of 10. These bacterial communities (microbiota) become a part of us from birth and participate in what is now regarded as a relationship of symbiotic mutualism, whereby the human provides a nutrient-enriched tailored living environment. In return, bacteria play a critical role for the health and development of the human species. There is evidence, for example, that the presence of the bacterial microbiome is integral for modulation of the human immune system, digestion of dietary nutrients otherwise impervious to human enzymes, and prevention of pathogenic bacterial disease. Given these observations, some go as far as to characterize the human and their corresponding microbiota as parts of a vastly greater superorganism. At a minimum, it is clear that mammals and microorganisms have coevolved to produce an intricate and vital symbiotic relationship.

Reminiscent of the inextricable linkage between the invention/popularization of the microscope and the discovery of microorganisms, both attributed to Van Leeuwenhoek (late seventeenth century), the recent charge to characterize whole populations of bacteria and viruses was permitted by advances in experimental techniques and laboratory sciences. These advances include advancements in bioinformatics, biological analytics, and DNA/RNA collection and sequencing techniques, which allow for high throughput approaches to specify and quantitate myriads of different bacteria. Although a single strain of bacteria may be held accountable as an etiologically specific cause for diseases, such as *Clostridium difficile* for pseudomembranous colitis, perhaps the more pertinent question is: what changes in the usually protective microbiome (dysbiosis) allowed for such infection? In that example, the answer is antibiotic-induced dysbiosis. Moreover, the state of microbiota has been associated with conditions such as diabetes, skin disease, obesity, inflammatory bowel disease (IBD), and even cancer, all of which are commonly regarded as noninfectious processes.

Although inflammatory, infectious, and neoplastic diseases are often considered categorically distinct processes, evidence has shown significant overlap between them. It is estimated that 15% of worldwide cancer is of infectious nature, with human papillomavirus, hepatitis B virus, hepatitis C virus, human herpesvirus 8, and *Helicobacter pylori* recognized as the definitive cause of cervical cancer, liver cancer, Kaposi sarcoma, and stomach cancer/lymphoma, respectively. Furthermore, direct causation of cancer by chronic inflammatory conditions is well documented. The association of IBD with increased risk of colon cancer is a case in point. Thus, it should come as no surprise that alterations of the microbiome may lead to infectious, inflammatory, and cancerous disease. The focus of this review is to detail the interrelationship between colorectal cancer (CRC) and the gut microbiome.

BACKGROUND

CRC is the second leading type of cancer in females and the third in males worldwide, with more than 1.2 million new cases and more than 600,000 estimated deaths in