Microbiota as a mediator of cancer progression and therapy

JILLIAN L. POPE, SARAH TOMKOVICH, YE YANG, and CHRISTIAN JOBIN

GAINESVILLE, FLA AND CHAPEL HILL, NC

Complex and intricate circuitries regulate cellular proliferation, survival, and growth, and alterations of this network through genetic and epigenetic events result in aberrant cellular behaviors, often leading to carcinogenesis. Although specific germline mutations have been recognized as cancer inducers, the vast majority of neoplastic changes in humans occur through environmental exposure, lifestyle, and diet. An emerging concept in cancer biology implicates the microbiota as a powerful environmental factor modulating the carcinogenic process. For example, the intestinal microbiota influences cancer development or therapeutic responses through specific activities (immune responses, metabolites, microbial structures, and toxins). The numerous effects of microbiota on carcinogenesis, ranging from promoting, preventing, or even influencing therapeutic outcomes, highlight the complex relationship between the biota and the host. In this review, we discuss the latest findings on this complex microbial interaction with the host and highlight potential mechanisms by which the microbiota mediates such a wide impact on carcinogenesis. (Translational Research 2017;179:139–154)

Abbreviations: AOM = azoxymethane; Apc = adenomatous polyposis coli; CAC = colitis associated cancer; CRC = colorectal cancer; DNA-PK = DNA-dependent protein kinase; GF = germ free; GI = gastrointestinal; IBD = inflammatory bowel diseases; IL = interleukin; MAIT = mucosa-associated invariant T; MTX = methotrexate; NLR = NOD-like receptor; NLRP1 = NLR family, pyrin domain containing 1; NOD = nucleotide-binding oligomerization domain-containing protein; PDL-1 = programmed cell death protein 1 ligand 1; PI3K = phosphoinositide 3-kinase; PRR = pattern recognition receptors; SCFA = short chain fatty acids; TIGIT = T cell immunoglobulin and ITIM domain; TLR = toll-like receptors; Tregs = regulatory T cells; WT = wild type

INTRODUCTION

Cancer is a multifactorial disease involving genetic and epigenetic alterations, environmental factors, and lifestyle components. Cancer genetic studies have offered a spectacular view of the complexity and intricacy of events at play during carcinogenic evolution.[1-3] Similarly, significant progress has been made on the identification and functional effect of environmental elements and lifestyles on tumorigenesis.[4] As a whole, these studies have contributed important knowledge regarding mechanisms implicated in cancer initiation, progression, metastasis, and therapeutic responses. Beside the previously mentioned factors, a relatively novel component named the microbiota has recently been recognized as a potent modulator of the carcinogenic process. The microbiota is a consortium of microorganisms composed of bacteria, viruses, fungi, and protozoa living in various body sites, including oral,[5] urogenital,[6] and gastrointestinal (GI) cavities,[7] forming a community living in a eubiotic state. Noteworthy, genetic, environmental, and lifestyle components all influence microbial composition and one should not view these as independent factors but rather as integrated components of

From the Department of Medicine, University of Florida, Gainesville, Fla; Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Infectious Diseases and Pathology, University of Florida, Gainesville, Fla.

Submitted for publication April 22, 2016; revision submitted July 18, 2016; accepted for publication July 20, 2016.

Reprint requests: Christian Jobin, 2033 Mowry Road, PO Box 103633, Gainesville, FL 32610; e-mail: christian.jobin@medicine.ufl.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.07.021

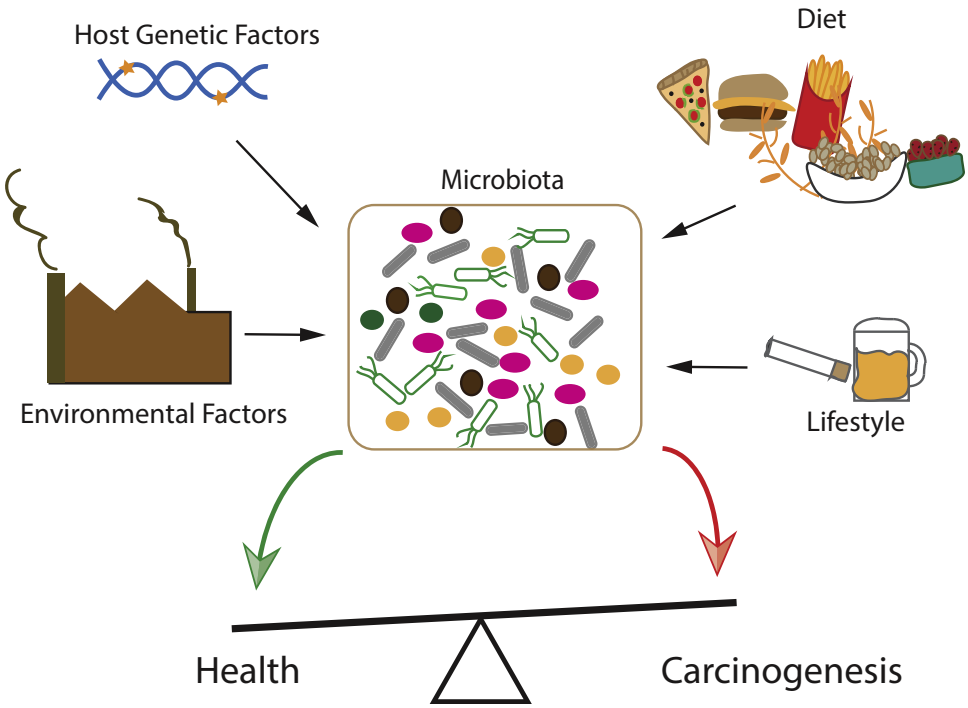

Fig 1. The microbiota regulates the balance between health and disease. A combination of external factors can influence microbial composition, including host genetics, diet, lifestyle, and environmental factors. These perturbations in the microbiota shift the balance between healthy and carcinogenesis.

carcinogenesis[8] (Fig 1). The vast majority of microorganisms reside within the intestine, and influence not only the local gut function but also exert long-distant effects on host homeostasis and disease states such as allergy, asthma,[9] rheumatoid arthritis,[10] cardiovascular diseases,[11] metabolic syndrome,[12] and obesity.[12,13] This review will focus on recent advances about the local and wide range effects the intestinal microbiota exerts as it mediates numerous phases of cancer, particularly colorectal cancer (CRC), spanning initiation, progression, and treatment.

The mechanisms by which the microbial community exerts such a profound and wide impact on the host are still unclear but likely originate from microbial metabolism and microbial-derived structures interacting with the host cellular compartment through receptors or receptor-independent fashion. Moreover, the identities of specific microorganisms responsible for health maintenance or disease development are still unclear and probably result from an ensemble of organisms rather than any particular one. A general consensus in the field is that alterations in the microbiome, a phenomenon termed dysbiosis, are often linked to disease development, including CRC.[14] In addition, preclinical models suggest that microbial dysbiosis has a causative impact on cancer development, at least for CRC. As such, some forms of cancer may be influenced by the action of a microbial community as opposed to a single organism paradigm as seen with *Helicobacter pylori* (gastric cancer), hepatitis B or C virus (liver cancer), or Epstein–Barr virus (lymphomas) infection.[15]

MICROBIAL DYSBIOSIS AND TUMORIGENESIS

Although numerous body sites have been shown to harbor a microbiota, the intestine has the most compelling evidence that microbial composition is linked to carcinogenesis. In this pathology, phylogenic differences were reported between bacteria present in the intestine of healthy subjects compared with CRC patients.[16] Microbial dysbiosis is also observed between tumor and healthy adjacent tissue of the same patient,[17] distal vs proximal tumors,[18] and between tumor staging from adenoma to adenocarcinoma.[19] A systematic review of reports documented microbial dysbiosis in CRC patients highlighting specific changes within the intestinal microbial community such as increased representation of fusobacteria, *Alistipes*, porphyromonadaceae, coriobacteridae, staphylococcaceae, *Akkermansia*, and methanobacteriales and decreased abundance of *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, *Faecalibacterium*, *Roseburia*, and *Treponema*.[14] In line with microbial dysbiosis, novel