Microbiome

Imran Khan[1]

[1] Department of Medical Oncology, Artemis Hospitals, Gurugram, Haryana, India

Address for correspondence Imran Khan, DrNB, Artemis Hospitals, Sector 52, Gurugram, 122018, Haryana, India (e-mail: 845docimran@gmail.com).

Ind J Med Paediatr Oncol 2021;42:461–465.

Introduction

Microbiota is the sum total of all organisms present in the human body. It includes bacteria, fungi, viruses, and other unicellular organisms. Microbiome is the combined genetic material from all microorganisms in a given host. The terms microbiome and microbiota are generally used interchangeably. As per the Human Microbiome Project, human microbiota harbors 10 to 100 trillion organisms. It means for every human cell, there are 10 times more microbes present. The microbiome is present in all parts of the body with the preponderance at the skin, oral cavity, lower gastrointestinal tract, upper respiratory tract, and genitourinary tract.[1,2]

As per the International Cancer Microbiome Consortium Meeting, various terms used in the study of microbiome are tabulated as in ►**Table 1**.

Evolution of Microbiome

After birth, the body is essentially sterile, that is, no microorganisms are present in the body. Afterward, the growth of facultative aerobes bacteria (*Enterobacteriaceae*) occurs in the gut. It is followed by growth of anaerobic species (*Clostridia* spp.). By the end of third year of life, the microbiome increases in composition and diversification and attains adult-type characteristics. *Firmicutes* and *Bacteroidetes* are the two most dominant bacterial phyla.[3,4] The composition of microbiome is influenced by the following factors.

Mode of Delivery of a Child

Children delivered by cesarean have largely different microbiome than those born vaginally.

Environmental Factors

The microbiome varies with race, gender, ethnicity, geography, diet, etc. For instance, Western lifestyle hampers the normal composition of the microbiome. Similarly, excessive use of antibiotics in neonates also prevents microbiome. Microbial biodiversity varies with various exogenous variables such as sex, race, and weight.

Race

Around 400 different genes have been described that distinguish the microbiome of people from different continents.[5]

Carcinogenesis Pathways Involved in Microbiome

Cellular DNA Damage

Gram-negative bacilli produce toxins (colibactin) or free radicals that cause lethal damage to normal DNA.[6]

Cancer Cell Proliferation

Escherichia coli induce growth factors that trigger cell growth.[7]

Chronic Inflammation

Helicobacter pylori infection leads to chronic inflammation (gastritis) and predisposes to gastric adenocarcinoma and gastric MALToma.[8]

Immune Dysregulation

Bacteroides fragilis influences T-helper cells (CD 4 cells) and triggers interleukin-mediated signals. Microbes hamper natural killer cell activity and reduce ability to kill cancer cells.[9]

DOI https://doi.org/10.1055/s-0041-1735599.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 Definitions used in the study of microbiome

Term	Definition
Microbiome	The combined genetic material from all microorganisms in a specified niche
Microbiota	All the microorganisms in a specified niche
Dysbiosis	Departure from the healthy microbiome state
Symbiont	An organism living closely with another
Mutualistic	An organism living closely with another and both organism benefit
Commensalistic	An organism living closely with another and one benefits while others are not benefited
Parasitic	An organism living closely with another and benefits by harming another
Amensalistic	An organism living closely with another and no benefit by harming another
Pathogen	A microorganism that can cause disease
Pathobiont	Microorganisms present in the microbiota that can cause disease
Pharmacomicrobiomics	The study of the interaction of host microbiome and drugs

Inducing Host Cell Proliferation

Human papillomavirus enters the host cell nucleus and takes control of DNA replication (by E 6 and E 7 genes) causing oncogenesis.[10]

Epithelial to Mesenchymal Transition

B. fragilis and *Fusobacterium nucleatum* cause damage to adhesion molecules between host cells, thus attaining invasive properties.[11]

Metastasis

Microbes produce special molecules that can influence gene expression with change in cell density. Gram-positive bacteria secrete small peptides and Gram-negative bacteria secrete lactones that contribute to metastasis.[12]

Alteration of Cell Epigenetics

a. *F. nucleatum* possesses virulence factors that drive cell proliferation (WNT/β-catenin pathway).
b. *Porphyromonas* sp. produces reactive oxygen species and *Bilophila* and *Fusobacterium* produce hydrogen sulfide that is linked with colorectal neoplasia.
c. Enterotoxigenic *B. fragilis* secretes toxins that cause colon cancer (TH-17/IL-17 pathway).
d. *E. coli* and *Campylobacter jejuni* produce genotoxins such as cytolethal distending toxin and colibactin that cause DNA damage.[13,14]

Microbiome and Cancer

a. Esophageal and gastric cancers: *H. pylori* infection results in gastric inflammation, achlorhydria, dysplasia, gastric cancer, and gastric lymphoma (MALToma). *H. pylori* reduces acid secretion that reduces acid reflux and decreases the chances of developing esophageal adenocarcinoma.
b. Gallbladder cancer: Salmonellosis predisposes to gallbladder cancer.
c. Hepatocellular carcinoma: Hepatitis B virus and Hepatitis C virus can infect the liver and cause cancer. In animal models, Gram-negative bacteria via inflammation pathway promote hepatocarcinogenesis.
d. Lung cancer: Various pulmonary infections such as *Mycobacterium tuberculosis* predispose to it.
e. Breast cancer: Various subtypes have a different composition of the microbiome. Furthermore, microbial variation is seen with different grades of breast cancer.
f. Lymphomas: *H. pylori*, a commensal in human stomach, has been incriminated in gastric marginal zone lymphoma and gastric adenocarcinoma.
g. Kaposi sarcoma-associated herpesvirus being the etiologic factor for Kaposi sarcoma and primary effusion lymphomas.
h. Other cancers: Human polyomaviruses—Merkel cell polyomavirus—leads to Merkel cell carcinoma and skin cancer. Simian Virus 40 (SV40) leads to mesothelioma.

Microbiome and Hallmarks of Cancer

Microbiome affects all hallmarks of cancer as described in ►**Table 2**.

Microbiome and Food

High-Fiber Diet

Plant-based diet is difficult to digest. Microorganisms present in gastrointestinal tract convert these poorly digestible into small fatty acids (butyrate and propionate) and other small compounds (phytochemicals, polyphenols, flavonoids, and glucosinolates). Butyrate and propionate favor cell differentiation, apoptosis, and regulation of glucose and lipid metabolism. It results in inhibition of tumorigenesis.[15] Microbes (e.g., *Eggerthella*) metabolize glucosinolates into isothiocyanates that have anticancer properties. Isoflavonoids also have anticancer properties.[16]

Protein- and Fat-Containing Foods

Consumption of protein- and fat-rich diets inhibits the content of beneficial microbes such as *Roseburia* and *Eubacterium rectale* and favors the production of carcinogens such as secondary bile acids and N-nitroso compounds. Animal-

Table 2 Microbiome and hallmarks of cancer[19]

Bacteria	Mechanism	Hallmark
Enterotoxigenic *Bacteroides fragilis*	*B. fragilis* toxin	Sustaining proliferative signals/genomic instability/ inflammation
Fusobacterium nucleatum	Fad A adhesin/Fap2 adhesin	Sustaining proliferative signals/avoiding immune destruction
Escherichia coli (pks +)	Colibactin	Genomic instability/sustaining proliferative signals
Enterococcus faecalis	Unknown	Genomic instability/mutation
Alistipes spp.	Unknown	Inflammation
Bifidobacterium	Unknown	Inhibits immune destruction
Bacteroides thetaiotaomicron	Unknown	Avoiding immune destruction

rich diets promote the production of bile-tolerant microbes and inhibit polysaccharide-metabolizing microbes that possibly increase the risk of cancer (►**Table 3**).[17]

Microbiome and Chemotherapy and Immunotherapy Drugs

There occur interactions between the microbiome and anticancer treatment at several levels, for example, by modulating the immune system and by metabolizing the chemotherapeutic drugs.[18] The effect of various anticancer drugs is given in ►**Table 4**.

Microbiome in HSCT and GVHD

The association between microbiome in hematopoietic stem cell transplant (HSCT) and graft versus host disease (GVHD) is now well established. The use of antibiotic prophylaxis reduces microbiome diversity within first 2 weeks after HSCT. Researchers have shown that certain microbial products such as short-chain fatty acids and indole-based derivatives play a role in the prevention of GVHD.

Cancer-related infections have direct bearing with microbial diversity. In patients of Acute Myeloid Leukemia, greater baseline diversity was associated with acquiring less chances of infections. Similarly, in Hodgkin lymphoma, bloodstream infection was worse in those with less microbial diversity. Some data are also accumulating regarding relationship between anti-vascular endothelial growth factor (VEGF) and type of microorganisms: higher *Bacteroides* being deleterious and higher *Prevotella* beneficial for anti-VEGF-related diarrhea.

Immunotherapy is new talk of the town in different end-stage cancers. Studies have proven that higher patients with higher microbial diversity show better response to immunotherapy.

Future Directions

The connection between cancer and microbiome is evolving and future studies are pipelined to discern causality and influence on therapeutics. Key directions for the future are as follows:

- Multicenter international longitudinal cohort studies.
- Uniformity in reporting microbiome research.

Table 3 Relationship between diet and microbiome

	Effect of diet with microorganism		
Beneficial	*Bifidobacterium longum*	Short-chain fatty acids	Maintain barrier function, tight junction, limit pathogen growth
	Lactobacillus acidophilus	Vitamin B12	Methylation and DNA histone modification
	Saccharomyces boulardii	Antioxidants, flavonoids glucosinolates	Prevent DNA damage slow tumorgenesis
Deleterious	*Salmonella enterica*	N-nitroso compounds secondary bile acids	Base pair shift, DNA alkylation
	Escherichia coli	Hydrogen sulfide	Decreases mucus formation, damages gastric mucosa
	Fusobacterium nucleatum	Free radical generation	Inflamed gut mucosa, disrupts intracellular junction

Table 4 Anticancer drugs and microbiome

Anticancer agents	Effect on microbiome
Anthracyclines	Synthesized by streptomyces strains WAC04685 causes deactivation of doxorubicin Anthracyclines are bacteriostatic to *Acinetobacter* species[20]
Cyclophosphamide	It causes damage to gut mucosa and makes the gut leaky. Gram-positive bacteria enter lymphoid organs causing alteration of the immune response[21]
SERM	Resistance to tamoxifen is influenced by microbiome[22]
Taxanes	They are metabolized by bacteria. Interfere with bacterial LPS. Alter microbiome[23]
Antimetabolite	5-FU and gemcitabine are metabolized by the microbiome. Probiotics prevent 5FU-induced mucositis. Intratumoral bacteria (Gamma proteobacteria) cause the deactivation of gemcitabine in colorectal cancer. Use of ciprofloxacin prevents it[24,25]
PARP inhibitor	They increase the diversity of the gut microbiome. *Bacteroides* and *Burkholderia* synergize the antitumor effect of PARP inhibitors[26]
Radiation therapy	The microbiome protects against the severity of radiation-induced mucositis[27]
Anti-CTLA-4 agents	Its efficacy is influenced by gut microbiome antibiotic-treated decreases its antitumor effect[28]
Anti-PD-1/PD-L1 agents	Antitumor immunity is enhanced in the presence of Bifidobacterium spp. In lung, kidney, skin cancers, the responder patients have higher α diversity in their fecal microbiome. Antibiotics use treatment hampers anti-PD-1 response[29]

Abbreviations: 5-FU, fluorouracil; anti-CTLA4, anti-cytotoxic T lymphocyte-associated protein 4; LPS, lipopolysaccharides; PARP, poly ADP ribose polymerase; PD-L1, programmed death ligand 1; PD, programmed death; SERM, selective estrogen receptor modulator.

- Human microbe—inoculation studies.
- Implementation of data in various oncology fields.

Financial Support and Sponsorship
Nil.

Conflicts of Interest
There are no conflicts of interest.

References

1 Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012;486 (7402):207–214
2 Rosner JL. Ten times more microbial cells than body cells in humans? Microbe 2014;9:47
3 Penders J, Gerhold K, Thijs C, et al. New insights into the hygiene hypothesis in allergic diseases: mediation of sibling and birth mode effects by the gut microbiota. Gut Microbes 2014;5(02): 239–244
4 Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics 2006; 118(02):511–521
5 Chen L, Zhang YH, Huang T, Cai YD. Gene expression profiling gut microbiota in different races of humans. Sci Rep 2016;6:23075
6 Nougayrède JP, Homburg S, Taieb F, et al. Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 2006;313 (5788):848–851
7 Cougnoux A, Dalmasso G, Martinez R, et al. Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. Gut 2014;63(12):1932–1942
8 Polk DB, Peek RM Jr. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer 2010;10(06):403–414
9 Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 2009;15(09):1016–1022
10 Williams VM, Filippova M, Soto U, Duerksen-Hughes PJ. HPV-DNA integration and carcinogenesis: putative roles for inflammation and oxidative stress. Future Virol 2011;6(01):45–57
11 Gaines S, Williamson AJ, Hyman N, Kandel J. How the microbiome is shaping our understanding of cancer biology and its treatment. Semin Colon Rectal Surg 2018;29:12–16
12 Wynendaele E, Verbeke F, D'Hondt M, et al. Crosstalk between the microbiome and cancer cells by quorum sensing peptides. Peptides 2015;64:40–48
13 Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504(7480):446–450
14 Liang L, Ai L, Qian J, Fang JY, Xu J. Long noncoding RNA expression profiles in gut tissues constitute molecular signatures that reflect the types of microbes. Sci Rep 2015;5:11763
15 Ríos-Covián D, Ruas-Madiedo P, Margolles A, Gueimonde M, de Los Reyes-Gavilán CG, Salazar N. Intestinal short chain fatty acids and their link with diet and human health. Front Microbiol 2016;7:185
16 Li F, Hullar MA, Schwarz Y, Lampe JW. Human gut bacterial communities are altered by addition of cruciferous vegetables to a controlled fruit- and vegetable-free diet. J Nutr 2009;139(09):1685–1691
17 Russell WR, Gratz SW, Duncan SH, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr 2011;93(05): 1062–1072
18 Bashiardes S, Tuganbaev T, Federici S, Elinav E. The microbiome in anti-cancer therapy. Semin Immunol 2017;32:74–81
19 Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog 2017;13(09):e1006480
20 Cox G, Koteva K, Wright GD. An unusual class of anthracyclines potentiate Gram-positive antibiotics in intrinsically resistant Gram-negative bacteria. J Antimicrob Chemother 2014;69(07):1844–1855
21 Yang J, Liu KX, Qu JM, Wang XD. The changes induced by cyclophosphamide in intestinal barrier and microflora in mice. Eur J Pharmacol 2013;714(1-3):120–124
22 Luxo C, Jurado AS, Custódio JB, Madeira VM. Toxic effects of tamoxifen on the growth and respiratory activity of Bacillus stearothermophilus. Toxicol In Vitro 2001;15(4-5):303–305
23 Zhou DJ, Pan J, Yu HL, Zheng GW, Xu JH. Target-oriented discovery of a new esterase-producing strain Enterobacter sp. ECU1107 for whole cell-catalyzed production of (2S,3R)-3-phenylglycidate as a chiral synthon of Taxol. Appl Microbiol Biotechnol 2013;97(14): 6293–6300

24 Vanlancker E, Vanhoecke B, Smet R, Props R, Van de Wiele T. 5-Fluorouracil sensitivity varies among oral micro-organisms. J Med Microbiol 2016;65(08):775–783
25 Vande Voorde J, Sabuncuoğlu S, Noppen S, et al. Nucleoside-catabolizing enzymes in mycoplasma-infected tumor cell cultures compromise the cytostatic activity of the anticancer drug gemcitabine. J Biol Chem 2014;289(19):13054–13065
26 Vida A, Kardos G, Kovács T, Bodrogi BL, Bai P. Deletion of poly(ADP—ribose) polymerase-1 changes the composition of the microbiome in the gut. Mol Med Rep 2018;18(05):4335–4341
27 Zhu XX, Yang XJ, Chao YL, et al. The potential effect of oral microbiota in the prediction of mucositis during radiotherapy for nasopharyngeal carcinoma. EBioMedicine 2017; 18:23–31
28 Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015;350 (6264):1079–1084
29 Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359(6371):97–103

