



# Microbiome

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## 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.<sup>1,2</sup>

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.<sup>3,4</sup> 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.<sup>5</sup>

## Carcinogenesis Pathways Involved in Microbiome

### Cellular DNA Damage

Gram-negative bacilli produce toxins (colibactin) or free radicals that cause lethal damage to normal DNA.<sup>6</sup>

### Cancer Cell Proliferation

*Escherichia coli* induce growth factors that trigger cell growth.<sup>7</sup>

### Chronic Inflammation

*Helicobacter pylori* infection leads to chronic inflammation (gastritis) and predisposes to gastric adenocarcinoma and gastric MALToma.<sup>8</sup>

### 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.<sup>9</sup>

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**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.<sup>10</sup>

### Epithelial to Mesenchymal Transition

*B. fragilis* and *Fusobacterium nucleatum* cause damage to adhesion molecules between host cells, thus attaining invasive properties.<sup>11</sup>

### 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.<sup>12</sup>

### Alteration of Cell Epigenetics

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

### Microbiome and Cancer

- 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.
- Gallbladder cancer: Salmonellosis predisposes to gallbladder cancer.
- 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.

- Lung cancer: Various pulmonary infections such as *Mycobacterium tuberculosis* predispose to it.
- Breast cancer: Various subtypes have a different composition of the microbiome. Furthermore, microbial variation is seen with different grades of breast cancer.
- Lymphomas: *H. pylori*, a commensal in human stomach, has been incriminated in gastric marginal zone lymphoma and gastric adenocarcinoma.
- Kaposi sarcoma-associated herpesvirus being the etiologic factor for Kaposi sarcoma and primary effusion lymphomas.
- 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.<sup>15</sup> Microbes (e.g., *Eggerthella*) metabolize glucosinolates into isothiocyanates that have anticancer properties. Isoflavonoids also have anticancer properties.<sup>16</sup>

#### 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<sup>19</sup>

Bacteria	Mechanism	Hallmark
Enterotoxigenic <i>Bacteroides fragilis</i>	<i>B. fragilis</i> toxin	Sustaining proliferative signals/genomic instability/inflammation
<i>Fusobacterium nucleatum</i>	Fad A adhesin/Fap2 adhesin	Sustaining proliferative signals/avoiding immune destruction
<i>Escherichia coli</i> (pks +)	Colibactin	Genomic instability/sustaining proliferative signals
<i>Enterococcus faecalis</i>	Unknown	Genomic instability/mutation
<i>Alistipes</i> spp.	Unknown	Inflammation
<i>Bifidobacterium</i>	Unknown	Inhibits immune destruction
<i>Bacteroides thetaiotaomicron</i>	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**).<sup>17</sup>

### Microbiome and Chemotherapy and Immunotherapy Drugs

There occur interactions between the microbiome and anti-cancer treatment at several levels, for example, by modulating the immune system and by metabolizing the chemotherapeutic drugs.<sup>18</sup> 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	<i>Bifidobacterium longum</i>	Short-chain fatty acids	Maintain barrier function, tight junction, limit pathogen growth
	<i>Lactobacillus acidophilus</i>	Vitamin B12	Methylation and DNA histone modification
	<i>Saccharomyces boulardii</i>	Antioxidants, flavonoids, glucosinolates	Prevent DNA damage slow tumorigenesis
Deleterious	<i>Salmonella enterica</i>	N-nitroso compounds secondary bile acids	Base pair shift, DNA alkylation
	<i>Escherichia coli</i>	Hydrogen sulfide	Decreases mucus formation, damages gastric mucosa
	<i>Fusobacterium nucleatum</i>	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 <i>Acinetobacter</i> species <sup>20</sup>
Cyclophosphamide	It causes damage to gut mucosa and makes the gut leaky. Gram-positive bacteria enter lymphoid organs causing alteration of the immune response <sup>21</sup>
SERM	Resistance to tamoxifen is influenced by microbiome <sup>22</sup>
Taxanes	They are metabolized by bacteria. Interfere with bacterial LPS. Alter microbiome <sup>23</sup>
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 <sup>24,25</sup>
PARP inhibitor	They increase the diversity of the gut microbiome. <i>Bacteroides</i> and <i>Burkholderia</i> synergize the antitumor effect of PARP inhibitors <sup>26</sup>
Radiation therapy	The microbiome protects against the severity of radiation-induced mucositis <sup>27</sup>
Anti-CTLA-4 agents	Its efficacy is influenced by gut microbiome antibiotic-treated decreases its antitumor effect <sup>28</sup>
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 $\alpha$ diversity in their fecal microbiome. Antibiotics use treatment hampers anti-PD-1 response <sup>29</sup>

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.

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