

## REVIEW ARTICLE

## Microbial architects of malignancy: Exploring the gut microbiome's influence in cancer initiation and progression

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## Abstract

The gut microbiome, a complex community of microorganisms residing in the gastrointestinal tract, has emerged as a critical player in cancer initiation and progression. This review provides an overview of the intricate interactions between the gut microbiome and cancer, exploring the underlying mechanisms and potential therapeutic implications. The gut microbiome exerts profound effects on the immune system, modulating immune responses, and chronic inflammation, which are pivotal in cancer development. In addition, it influences metabolism by altering nutrient metabolism and producing metabolites that can directly impact cellular processes related to cancer progression. Furthermore, certain gut bacteria can induce DNA damage or modify DNA repair mechanisms, contributing to the initiation and promotion of cancer. Moreover, the gut microbiome can significantly influence the effectiveness and toxicity of anticancer therapies, potentially affecting treatment outcomes. Understanding these complex interactions holds promise for the development of strategies that target the gut microbiome to prevent and treat cancer more effectively. This review emphasizes the clinical relevance of the gut microbiome in cancer, including the identification of microbial biomarkers for cancer diagnosis and prognosis. Furthermore, it discusses potential challenges and future directions for research in this rapidly evolving field. Overall, unraveling the role of the gut microbiome in cancer initiation and progression provides valuable insights for advancing personalized cancer treatment and improving patient outcomes.

**Keywords:** Microbiome; Cancer; Initiation; Progression

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## 1. Introduction

The gut microbiome, a diverse and dynamic ecosystem of microorganisms inhabiting the gastrointestinal tract, has gained increasing recognition for its influential role in human health and disease.<sup>1,2</sup> Emerging evidence suggests that the gut microbiome plays

a significant role in cancer initiation and progression, with implications for diagnosis, treatment, and prevention.<sup>3</sup> It has an enormous effect on how the immune system functions and chronic inflammation and immunological dysregulation are both linked to dysbiosis, an imbalance in the gut microbial community.<sup>4</sup> Chronic inflammation is a well-established hallmark of cancer development, and the gut microbiome's ability to modulate immune responses can have far-reaching consequences.<sup>5</sup> Studies have demonstrated that specific microbial taxa or metabolites can either promote or suppress inflammation, affecting the tumor microenvironment and potentially triggering the onset and progression of cancer.<sup>6,7</sup>

Another important area where the gut microbiota has an impact is metabolism. The breakdown and absorption of dietary components, which affect nutritional availability and energy metabolism, are greatly influenced by gut bacteria.<sup>8,9</sup> Dysbiosis in the gut microbiome can disrupt metabolic homeostasis, leading to alterations in metabolite profiles that may promote carcinogenesis.<sup>10,11</sup> Certain gut bacteria can produce metabolites that directly cause genotoxicity or have an impact on cellular functions such as DNA repair and apoptosis, which can affect the progression of cancer.<sup>4,12</sup>

Besides, the modification of therapeutic efficacy and toxicity in drugs for cancer has been linked to the gut flora. Chemotherapeutic drugs can be metabolized by gut flora, which can affect the bioavailability and potency of the drugs.<sup>13</sup> In addition, the toxicological spectra of anticancer drugs can be altered by gut microbial metabolites, which may affect treatment results and patient tolerability.<sup>14</sup> To improve therapeutic approaches and patient outcomes, it is crucial to comprehend these relationships.

Obviously, there is intriguing potential for clinical translation and personalized treatment in the realm of gut microbiome research on cancer onset and progression.<sup>15</sup> It might be possible to enhance cancer diagnosis, prognosis, and treatment selection by locating microbial biomarkers linked to certain cancer kinds or stages.<sup>16</sup> As a complementary therapeutic strategy for preventing or treating cancer, targeting the gut microbiome through dietary changes, probiotics, prebiotics, or fecal microbiota transplantation (FMT) shows promise.<sup>17,18</sup> By examining the intricate relationships between the gut microbiome and cancer, this review hopes to shed light on the underlying processes and possible treatment options.

## 2. An overview of gut microbial influences on cancer initiation

The gut microbiota influences the immune system, inflammation, and metabolism, which in turn influences metabolism and cancer development. The balance between

pro-inflammatory and anti-inflammatory responses is modulated by the gut microbiota, which has an impact on the immune system and creates a pro-tumorigenic environment.<sup>19-21</sup> Dysbiosis, which is characterized by an imbalance in the composition of the gut's microorganisms, has been found to be associated with such cases. In addition, the gut microbiome can produce metabolites, such as secondary bile acids and, as mentioned earlier, genotoxic substances, that promote DNA damage and oncogenic transformation (Table 1).<sup>22,23</sup>

The gut microbiome also influences the efficacy of anticancer therapies, such as immunotherapy, by modulating the host immune response and the tumor microenvironment.<sup>24,25</sup> Certain gut bacteria produce metabolites that can directly damage DNA or affect cellular processes related to cancer development. For instance, some bacteria produce enzymes that activate procarcinogens or generate metabolites that promote tumor growth.<sup>26</sup> Furthermore, gut flora influences metabolism by altering food component breakdown and absorption. Imbalances in gut flora can change food metabolism, resulting in increased synthesis of toxic metabolites or a lack of helpful chemicals, both of which may contribute to the onset of cancer.<sup>7,27</sup> Again, some bacteria can metabolize chemotherapy drugs, alter their effectiveness, and modify their toxicity, potentially hampering treatment outcomes.<sup>12</sup>

Our understanding of the complex interactions between the gut microbiome and cancer initiation is rapidly evolving. By studying these interactions, researchers can develop strategies that can modulate the gut microbiome to prevent or treat cancer more effectively.<sup>28</sup>

## 3. Mechanisms of cancer initiation by gut microbiome

The development and occurrence of cancer are significantly influenced by the gut microbiome.<sup>38</sup> It influences the immune system, inflammation, and metabolism, which are key factors in cancer development. The role of the microbiome in cancer progression is multifaceted and involves various mechanisms that can influence tumor growth, metastasis, and response to therapy.<sup>49</sup>

### 3.1. Modulation of tumor microenvironment

The role of the microbiome in tumor microenvironment modulation is crucial in the context of cancer initiation and progression.<sup>50</sup> Through a variety of methods, the microbiome can affect immune responses and inflammation in the tumor microenvironment.<sup>5</sup> For instance, certain bacterial species have been associated with promoting a pro-inflammatory environment that facilitates tumor growth and metastasis.<sup>24</sup> The modulation of tumor

**Table 1. Possible mechanisms underlying the orchestration of cancer initiation and progression by gut microbiome**

Type of cancer	Influence of gut microbiome	Examples	References
Colorectal cancer	Gut bacteria produce genotoxic substances (e.g., nitrosamines)	<i>Fusobacterium nucleatum</i> , <i>Bacteroides fragilis</i> , <i>Streptococcus gallolyticus</i> , and <i>Enterococcus faecalis</i>	26,29-33
	Dysbiosis alters DNA repair mechanisms		
	Microbial metabolites promote inflammation and tumorigenesis		
Gastric cancer	<i>Helicobacter pylori</i> infection is associated with gastric carcinogenesis	<i>Helicobacter pylori</i> , Epstein-Barr virus (EBV), <i>Streptococcus gallolyticus</i> , and <i>Lactobacillus johnsonii</i>	34-38
	Altered gut microbiota composition is linked to gastric cancer risk		
	Microbial dysbiosis influences inflammation and tissue damage		
Hepatocellular carcinoma	Dysbiosis contributes to liver inflammation and cancer development	Hepatitis B virus (HBV), Hepatitis C virus (HCV), gut microbiota dysbiosis	3,23,39-42
	Gut bacteria produce toxic metabolites (e.g., secondary bile acids)	<i>Helicobacter hepaticus</i>	
	Altered gut microbial metabolism affects liver carcinogenesis		
Pancreatic cancer	Distinct gut microbial profiles are associated with pancreatic cancer	<i>Porphyromonas gingivalis</i> , <i>Streptococcus gallolyticus</i> , <i>Helicobacter pylori</i> , <i>Fusobacterium nucleatum</i> , and <i>Gemella spp.</i>	43-48
	Gut bacteria promote local and systemic inflammation		
	Microbial dysbiosis affects immune responses and tumor progression		

microenvironment by microbiome highlights its potential impact on cancer progression and the need for further investigation in this area.

### 3.2. Regulation of immune response

The microbiome has a substantial impact on the regulation of immune-mediated responses, which influences the development and advancement of cancer. The gut microbiome has been shown to influence systemic immune activation and modulate the efficacy of immunotherapies.<sup>49</sup> The immunological landscape can be shaped by particular bacterial species of the microbiome, which can influence how the immune system responds to cancer cells and how the immunotherapeutic treatments work effectively.<sup>24</sup> Outlining the mechanisms behind cancer initiation and progression requires an understanding of the intricate interactions between the gut microbiome and immune response regulation.

### 3.3. Metabolite production and metabolic interactions

The microbiome exerts its influence on cancer initiation and progression through metabolite production and metabolic interactions.<sup>51</sup> One prominent example is the production of short-chain fatty acids (SCFAs) by gut bacteria, which have been shown to have both tumor-promoting and tumor-inhibiting effects, impacting various aspects of cancer, including growth, apoptosis,

and immune responses.<sup>52</sup> In addition, certain metabolites produced by the gut microbiota, such as trimethylamine-N-oxide, have been associated with promoting metastasis in specific cancer types, such as hepatocellular carcinoma.<sup>40</sup> Understanding the complex metabolic interactions between the gut microbiome and host metabolism is essential for unraveling the role of the microbiome in cancer initiation and progression.

### 3.4. Modulation of therapy response

The microbiome plays a significant role in modulating therapy response in cancer patients. The composition and diversity of the gut microbiome are associated with the efficacy and toxicity of various cancer treatments, including chemotherapy, immunotherapy, and targeted therapy.<sup>24</sup> Specific microbial species and their metabolites can interact with drugs, influencing their bioavailability, metabolism, and overall therapeutic outcomes. Furthermore, the gut microbiota may affect how effectively immunotherapies function by influencing systemic immune responses.<sup>49</sup> Understanding the complex interplay between the gut microbiome and therapy response is crucial for optimizing treatment strategies and developing personalized approaches for cancer patients.

### 3.5. Gut microbiome-host interactions

The modulation of interactions between the microbiome and the host, which in turn affects cancer occurrence and

progression, is greatly influenced by the gut microbiota. The microbiome-host interactions influence various aspects, including immune responses, inflammation, and metabolism.<sup>48</sup> For instance, the gut microbiome can shape the immune landscape and influence the activation and response of the host's immune system.<sup>49</sup> In addition, metabolic interactions between the microbiome and the host can lead to the production of metabolites that can either promote or inhibit tumorigenesis.<sup>52</sup> Determining the processes underlying cancer initiation and progression requires an understanding of the complex relationships between the gut microbiota and host interactions.

#### 4. The role of gut microbiome in DNA damage-mediated carcinogenesis

Due to its propensity to produce genotoxic chemicals and modify DNA repair processes, the gut microbiome may play an important role in DNA damage and may play a part in the development and propagation of cancer. The development of cancer is facilitated by dysbiosis in the gut microbial community, which can result in the release of genotoxic chemicals or changes to DNA repair pathways. Studies have demonstrated that specific gut bacteria can induce DNA damage through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).<sup>53</sup> These genotoxic substances can directly damage DNA, leading to mutations and genomic instability.<sup>54</sup> For instance, certain gut bacteria produce nitrosamines, which are recognized carcinogens that can damage DNA and promote tumor growth.<sup>13</sup>

Furthermore, the gut microbiome can influence DNA repair mechanisms, which are essential for maintaining genomic integrity. Dysbiosis is associated with alterations in DNA repair pathways, including the base excision repair and mismatch repair systems.<sup>55,56</sup> These dysregulated repair mechanisms can result in the accumulation of DNA damage and an increased risk of cancer development.

Knowing how the gut microbiota affects DNA damage that causes cancer can shed light on the mechanisms underlying cancer's inception and recurrence. To prevent or lessen the genotoxic effects of the gut microbiome, tailored therapies that target particular bacterial species or metabolites that cause DNA damage should be designed.

#### 5. Gut microbiome in anticancer therapies

Targeting the gut microbiome holds considerable potential in cancer prevention and treatment. By modulating the composition and functionality of the gut microbiome, it is possible to influence various processes involved in cancer initiation and progression.<sup>57</sup> Several approaches can be explored to leverage the gut microbiome for cancer prevention and treatment (Table 2).

**Table 2. Potential use of gut microbiome as anticancer therapies**

Cancer type	Examples of using gut microbiome as anticancer therapy	References
Colorectal cancer	Fecal microbiota transplantation to modulate the gut microbiome	58
Melanoma	Administration of specific probiotic strains to enhance the efficacy of immunotherapy	61
Lung cancer	Modulating the gut microbiome to improve response to immune checkpoint inhibitors	29
Breast cancer	Using prebiotics to expand the population of beneficial gut microbiome	62
Prostate cancer	Synbiotic therapy to enhance treatment response and reduce side effects	60
Pancreatic cancer	Modulating the gut microbiome to improve chemotherapy efficacy	49

- (i) Probiotics and prebiotics: Probiotics are live bacteria that confer health benefits, while prebiotics are substances that promote the growth of beneficial bacteria. These interventions can help restore microbial balance, enhance immune responses, and inhibit the accumulation of potential carcinogens.<sup>16</sup>
- (ii) FMT: FMT involves transferring fecal matter from a healthy donor to a recipient. This technique can restore a healthy gut microbiome and has shown promise in managing certain cancers and improving treatment outcomes.<sup>58</sup>
- (iii) Dietary modifications: Dietary interventions, such as adopting a high-fiber diet, can promote the growth of beneficial bacteria and enhance the production of SCFAs, which have anti-inflammatory and anti-cancer properties.<sup>59</sup>
- (iv) Antibiotics and microbial modulation: Targeted use of antibiotics can selectively deplete harmful bacteria associated with cancer progression. In addition, microbial modulation approaches, such as using bacteriophages or small molecules, can selectively target-specific microbial populations.<sup>28</sup>
- (v) Personalized approaches: Understanding an individual's gut microbiome composition and its interaction with cancer is a prerequisite for developing personalized interventions, which allow for more precise and effective cancer prevention and treatment strategies.<sup>60</sup>

Targeting the gut microbiome can regulate inflammation, immunological responses, and metabolism in the fight against cancer. However, further research is needed to optimize these approaches, establish their safety and efficacy, and determine their long-term effects.

## 6. Challenges

The application of gut microbiome as an anti-cancer therapy presents several challenges. The challenges described below need to be considered before applying gut microbiome as part of cancer therapeutic interventions.

- (i) Interindividual variability: The composition and functionality of the gut microbiome vary significantly among individuals, making it challenging to establish universal therapeutic approaches.<sup>29</sup>
- (ii) Microbiome dynamics: The gut microbiome is highly dynamic and its composition changes in response to various factors, including diet, medications, and disease states, posing a challenge to maintaining the desired microbial profiles.<sup>58</sup>
- (iii) Clinical translation: Translating findings from preclinical studies to clinical applications requires further research to explore the optimal treatment protocols and to enhance the safety and efficacy of the treatments.<sup>60</sup>
- (iv) Safety concerns: Modulating the gut microbiome can have unintended consequences and potential side effects, necessitating careful monitoring and evaluation.<sup>49</sup>

## 7. Future perspectives

The exploration of the gut microbiome's influence on cancer initiation and progression offers exciting opportunities for improving precision medicine, developing novel therapies, and fostering a deeper understanding of the intricate relationship between our microbiome and cancer. The future perspectives in this regard are outlined in the following:

- (i) Personalized approaches: Tailoring gut microbiome-based therapies to individual patients can improve treatment outcomes, after considering the specific microbial composition and disease characteristics unique to each individual.<sup>61</sup>
- (ii) Combination therapies. Exploring the synergistic effects of combining gut microbiome interventions with conventional cancer therapies, such as chemotherapy or immunotherapy, holds promise for enhanced treatment efficacy.<sup>62</sup>
- (iii) Precision medicine. Utilizing advanced techniques, such as metagenomics and metabolomics, allows for a deeper understanding of microbial interactions, which is essential for the development of targeted therapies.<sup>58</sup>
- (iv) Long-term monitoring. Longitudinal studies should be conducted to monitor the dynamic changes in the gut microbiome during treatment, and the study findings are instrumental for optimizing therapeutic strategies and predicting treatment responses.<sup>29</sup>

## 8. Conclusion

The gut microbiota influences immune responses, metabolism, and anticancer therapy, and so plays an important role in cancer development and progression. The influence of the gut microbiome on the metabolism and synthesis of genotoxic chemicals or procarcinogen-metabolizing enzymes highlights its significance in cancer development. Thus, a clear understanding of the complex interactions between the gut microbiome and cancer is a crucial requirement for designing effective therapeutic approaches.

Identifying microbial biomarkers linked to certain cancer types or stages can help with early identification, prognosis, and treatment selection. Using dietary treatments, probiotics, or FMT to target the gut microbiome could affect the gut microbial ecology and potentially prevent or modify cancer development. However, the implementation of gut microbiome-based treatments is constrained by the complexity and inter-individual variability of the gut microbiota and the need for standardized techniques; therefore, larger-scale investigations aiming to address these limitations should be conducted. In addition, more studies are needed to decipher the complex mechanisms behind the gut microbiome-cancer axis and to devise novel anticancer tactics involving the microbiome.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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## References

1. Plottel CS, Blaser MJ. Microbiome and malignancy. *Cell Host Microbe*. 2011;10:324-335.  
doi: 10.1016/j.chom.2011.10.003
2. Yu J, Feng Q, Wong SH, *et al*. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut*. 2017;66:70-78.  
doi: 10.1136/gutjnl-2015-309800
3. Ren Z, Li A, Jiang J, *et al*. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. *Gut*. 2019;68:1014-1023.  
doi: 10.1136/gutjnl-2017-315084
4. Ma C, Han M, Heinrich B, *et al*. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science*. 2018;360:eaan5931.  
doi: 10.1126/science.aan5931
5. Arthur JC, Gharaibeh RZ, Mühlbauer M, *et al*. Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer. *Nat Commun*. 2014;5:4724.  
doi: 10.1038/ncomms5724
6. Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. *CA Cancer J Clin*. 2017;67:326-344.  
doi: 10.3322/caac.21398
7. Dapito DH, Mencin A, Gwak GY, *et al*. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. *Cancer Cell*. 2012;21:504-516.  
doi: 10.1016/j.ccr.2012.02.007
8. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*. 2006;47:241-259.  
doi: 10.1194/jlr.R500013-JLR200
9. Fuhrman BJ, Feigelson HS, Flores R, *et al*. Associations of the fecal microbiome with urinary estrogens and estrogen metabolites in postmenopausal women. *J Clin Endocrinol Metab*. 2014;99:4632-4640.  
doi: 10.1210/jc.2014-2222
10. Gonzalez CA, Travier N, Luján-Barroso L, *et al*. Dietary factors and in situ invasive cervical cancer risk in the European prospective investigation into cancer and nutrition study. *Int J Cancer*. 2010;129:449-459.  
doi: 10.1002/ijc.25679
11. Midtvedt T. Microbial bile acid transformation. *Am J Clin Nutr*. 1974;27:1341-1347.  
doi: 10.1093/ajcn/27.11.1341
12. Flemer B, Warren RD, Barrett MP, *et al*. The oral microbiota in colorectal cancer is distinctive and predictive. *Gut*. 2017;67:1454-1463.  
doi: 10.1136/gutjnl-2017-314814
13. Loh YH, Jakszyn P, Luben RN, Mulligan AA, Mitrou PN, Khaw KT. N-nitroso compounds and cancer incidence: The European prospective investigation into cancer and nutrition (EPIC)-Norfolk study. *Am J Clin Nutr*. 2011;93:1053-1061.  
doi: 10.3945/ajcn.111.012377
14. Donia MS, Fischbach MA. HUMAN MICROBIOTA. Small molecules from the human microbiota. *Science*. 2014;349:1254766.  
doi: 10.1126/science.1254766
15. Azevedo MM, Pina-Vaz C, Baltazar F. Microbes and cancer: Friends or faux? *Int J Mol Sci*. 2020;21:3115.  
doi: 10.3390/ijms21093115
16. Grivnenkov SI, Wang K, Mucida D, *et al*. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature*. 2012;491:254-258.  
doi: 10.1038/nature11465
17. Plaza-Díaz J, Ruiz-Ojeda FJ, Vilchez-Padial LM, Gil A. Evidence of the anti-inflammatory effects of probiotics and synbiotics in intestinal chronic diseases. *Nutrients*. 2017;9:555.  
doi: 10.3390/nu9060555
18. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. *Science*. 2021;371:eabc4552.  
doi: 10.1126/science.abc4552
19. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157:121-141.  
doi: 10.1016/j.cell.2014.03.011
20. Ge Y, Wang X, Guo Y, *et al*. Gut microbiota influence tumor development and alter interactions with the human immune system. *J Exp Clin Cancer Res*. 2021;40:42.  
doi: 10.1186/s13046-021-01845-6
21. Dohlman AB, Klug J, Mesko M, *et al*. A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors. *Cell*. 2022;185:3807-3822.e12.  
doi: 10.1016/j.cell.2022.09.015
22. Kostic AD, Chun E, Robertson L, *et al*. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe*. 2013;14:207-215.  
doi: 10.1016/j.chom.2013.07.007
23. Yoshimoto S, Loo TM, Atarashi K, *et al*. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature*. 2013;499:97-101.

- doi: 10.1038/nature12347
24. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell*. 2018;33:570-580.  
doi: 10.1016/j.ccell.2018.03.015
  25. Routy B, Le Chatelier E, Derosa L, *et al*. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359:91-97.  
doi: 10.1126/science.aan3706
  26. Belcheva A, Irrazabal T, Robertson SJ, *et al*. Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. *Cell*. 2014;158:288-299.  
doi: 10.1016/j.cell.2014.04.051
  27. Bertocchi A, Carloni S, Ravenda PS, *et al*. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. *Cancer Cell*. 2021;39:708-724.e11.  
doi: 10.1016/j.ccell.2021.03.004
  28. Liu J, Zhang Y. Intratumor microbiome in cancer progression: Current developments, challenges and future trends. *Biomark Res*. 2022;10:37.  
doi:10.1186/s40364-022-00381-5
  29. Arthur JC, Perez-Chanona E, Muhlbauer M, *et al*. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science*. 2012;338:120-123.  
doi: 10.1126/science.1224820
  30. Zackular JP, Rogers MA, Ruffin MT 4th, *et al*. The human gut microbiome as a screening tool for colorectal cancer. *Cancer Prev Res (Phila)*. 2014;7:1112-1121.  
doi:10.1158/1940-6207.CAPR-14-0129
  31. Drewes JL, White JR, Dejea CM, *et al*. High-resolution bacterial 16s rRNA gene profile meta-analysis and biofilm status reveal common colorectal cancer consortia. *NPJ Biofilms Microbiomes*. 2017;3:34.  
doi: 10.1038/s41522-017-0040-3
  32. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. *Cell Host Microbe*. 2014;15:317-328.  
doi: 10.1016/j.chom.2014.02.007
  33. Yang Q, Wang B, Zheng Q, *et al*. A review of gut microbiota-derived metabolites in tumor progression and cancer therapy. *Adv Sci (Weinh)*. 2023;10:e2207366.  
doi: 10.1002/advs.202207366
  34. Yamaoka Y. Mechanisms of disease: *Helicobacter pylori* virulence factors. *Nat Rev Gastroenterol Hepatol*. 2010;7:629-641.  
doi: 10.1038/nrgastro.2010.154
  35. Amieva M, Peek RM Jr. Pathobiology of *Helicobacter pylori*-induced gastric cancer. *Gastroenterology*. 2016;150:64-78.  
doi: 10.1053/j.gastro.2015.09.004
  36. Eun CS, Kim BK, Han DS, *et al*. Differences in gastric mucosal microbiota profiling in patients with chronic gastritis, intestinal metaplasia, and gastric cancer using pyrosequencing methods. *Helicobacter*. 2014;19:407-416.  
doi: 10.1111/hel.12145
  37. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, *et al*. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut*. 2018;67:226-236.  
doi: 10.1136/gutjnl-2017-314205
  38. Wang L, Zhou J, Xin Y, *et al*. Bacterial overgrowth and diversification of microbiota in gastric cancer. *Eur J Gastroenterol Hepatol*. 2016;28:261-266.  
doi: 10.1097/MEG.0000000000000542
  39. Yu LX, Schwabe RF. The gut microbiome and liver cancer: Mechanisms and clinical translation. *Nat Rev Gastroenterol Hepatol*. 2017;14:527-539.  
doi: 10.1038/nrgastro.2017.72
  40. Yoshimoto S, Okada Y, Suzuki K, *et al*. Gut microbiota-dependent metabolite trimethylamine-N-oxide promotes metastasis of hepatocellular carcinoma. *Cancer Sci*. 2021;112:4534-4544.
  41. Ganesan R, Yoon SJ, Suk KT. Microbiome and metabolomics in liver cancer: Scientific technology. *Int J Mol Sci*. 2023;24:537.  
doi: 10.3390/ijms24010537
  42. Moreno-Gonzalez M, Beraza N. The role of the microbiome in liver cancer. *Cancers (Basel)*. 2021;13:2330.  
doi: 10.3390/cancers13102330
  43. Riquelme E, Zhang Y, Zhang L, *et al*. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. *Cell*. 2019;178:795-806.e12.  
doi: 10.1016/j.cell.2019.07.008
  44. Thomas RM, Jobin C. The microbiome and cancer: Is the 'oncobiome' mirage real? *Trends Cancer*. 2015;1:24-35.  
doi: 10.1016/j.trecan.2015.07.00
  45. Pushalkar S, Hundeyin M, Daley D, *et al*. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discov*. 2018;8:403-416.  
doi: 10.1158/2159-8290.CD-17-1134
  46. Aykut B, Pushalkar S, Chen R, *et al*. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature*. 2019;574:264-267.  
doi: 10.1038/s41586-019-1608-2
  47. Geller LT, Barzily-Rokni M, Danino T, *et al*. Potential

- role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science*. 2017;357:1156-1160.  
doi: 10.1126/science.aah5043
48. Sethi V, Vitiello GA, Saxena D, Miller G, Dudeja V. The role of the microbiome in immunologic development and its implication for pancreatic cancer immunotherapy. *Gastroenterology*. 2019;156:2097-2115.e2.  
doi: 10.1053/j.gastro.2018.12.045
  49. Vétizou M, Pitt JM, Daillère R, *et al.* Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science*. 2015;350:1079-1084.  
doi: 10.1126/science.aad1329
  50. Fu A, Yao B, Dong T, *et al.* Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. *Cell*. 2022;185:1356-1372.e26.  
doi: 10.1016/j.cell.2022.02.027
  51. Wang Y, Du J, Wu X, *et al.* Crosstalk between autophagy and microbiota in cancer progression. *Mol Cancer*. 2021;20:163.  
doi: 10.1186/s12943-021-01461-0
  52. Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Mol Cell*. 2012;48:612-626.  
doi: 10.1016/j.molcel.2012.08.033
  53. Polk DB, Peek RM Jr. *Helicobacter pylori*: Gastric cancer and beyond. *Nat Rev Cancer*. 2010;10:403-414.  
doi: 10.1038/nrc2857
  54. Nougayrede JP, Homburg S, Taieb F, *et al.* *Escherichia coli* induces DNA double-strand breaks in eukaryotic cells. *Science*. 2006;313:848-851.  
doi: 10.1126/science.1127059
  55. Wilson MR, Jiang Y, Villalta PW, *et al.* The human gut bacterial genotoxin colibactin alkylates DNA. *Science*. 2019;363:eaar7785.  
doi: 10.1126/science.aar7785
  56. Kostic AD, Gevers D, Pedamallu CS, *et al.* Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res*. 2012;22:292-298.  
doi: 10.1101/gr.126573.111
  57. Yang L, Li A, Wang Y, *et al.* Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. *Signal Transduct Target Ther*. 2023;8:35.  
doi: 10.1038/s41392-022-01304-4
  58. Biazzo M, Deidda G. Fecal microbiota transplantation as new therapeutic avenue for human diseases. *J Clin Med*. 2022;11:4119.  
doi: 10.3390/jcm11144119
  59. Zhang X, Li H, Lv X, *et al.* Impact of diets on response to immune checkpoint inhibitors (ICIs) therapy against tumors. *Life (Basel)*. 2022;12:409.  
doi: 10.3390/life12030409
  60. Singh NK, Beckett JM, Kalpurath K, Ishaq M, Ahmad T, Eri RD. Synbiotics as supplemental therapy for the alleviation of chemotherapy-associated symptoms in patients with solid tumours. *Nutrients*. 2023;15:1759.  
doi: 10.3390/nu15071759
  61. Sivan A, Corrales L, Hubert N, *et al.* Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350:1084-1089.  
doi: 10.1126/science.aac4255
  62. Slizewska K, Markowiak-Kopec P, Slizewska W. The role of probiotics in cancer prevention. *Cancers (Basel)*. 2021;13:20.  
doi: 10.3390/cancers13010020