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Review

Microbial influences on cancer: Mechanisms and implications

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ABSTRACT

Research on the connection between cancer and the microbiota has become crucial, emphasizing how microbial populations affect the onset, spread, and response to cancer therapy. The microbiota, especially the gut microbiota, is essential for regulating metabolism, inflammatory pathways, and immunological responses which are fundamental to cancer biology. According to studies, some microbial species may have preventive effects while others may encourage the formation of tumors. Through the production of genotoxins and other metabolites, the microbial composition can directly influence carcinogenesis; indirectly, it can influence immune responses and alter the tumor microenvironment. Furthermore, it has been discovered that the microbiota affects the toxicity and effectiveness of cancer treatments such as radiation, chemotherapy, and immunotherapy. A possible therapeutic strategy to enhance the results of cancer treatment is altering the microbiota by nutrition, probiotics, prebiotics, or fecal microbiota transplants. An outline of the complex relationships between cancer and the microbiota is given in this review, highlighting the need for more research to develop microbiome-targeted cancer prevention and treatment options.

Keywords: Cancer, immunomodulation, inflammation, microbiota.

The human body's surface barriers are home to diverse groups of bacteria, yeast, fungi, protozoa, archaea, and viruses. These bacteria collectively form the human microbiota, and the human microbiome is the collection of their genomes. The human microbiome encodes functions that are vital in many aspects of human physiology. For example, the gut microbiota regulates host metabolism and guides immune system growth and function.[1] A plethora of evidence supports the significance of microbiota in a variety of physical problems, including gastrointestinal, neurological, and cardiovascular disorders. Furthermore, studies have linked the role of microbiota with cancer and supported its significance in practically every facet of carcinogenesis, from cancer susceptibility and progression to anticancer therapy response. The literature suggests that correcting microbiota dysbiosis with good probiotic bacteria can benefit a wide range of cancer types. Furthermore, numerous microorganisms have been discovered to have anticancer properties and are being researched for use in cancer treatment. Several bacteria have been linked to cancer formation, including *Helicobacter pylori (H. pylori)*, which the World Health Organization classifies as a class I carcinogen and is involved with stomach adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. *Chlamydia trachomatis, Escherichia coli,* and *Salmonella enterica* have all been associated with cervical, colorectal, and gallbladder cancer, respectively. Furthermore, microbiota dysbiosis, which involves the control of several microbiome species, has been linked to cancer development.[2] Mechanistic studies of gut microbiota-immune system interactions have revealed that they have a significant impact on both innate and adaptive immunity by modifying primary and secondary lymphoid tissue activities that combat cancer and tumor immune surveillance. Many of these routes include toll-like receptor (TLR)-mediated cytokine signaling, but microbial metabolic effects on dietary energy harvesting, short-chain fatty acid

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(SCFA) synthesis, and antigenic mimicry by cancer cells are also important. In preclinical models, microbial metabolites influence the phenotypes of tumor somatic mutations and the efficacy of immune checkpoint inhibitors.[3] Accumulating evidence supports the gut microbiome's functional role in cancer development and progression, as well as its role in determining the efficacy and toxicity of chemotherapeutic agents (5-fluorouracil, cyclophosphamide, irinotecan, oxaliplatin, gemcitabine, methotrexate) and immunotherapeutic compounds [anti-programmed death ligand 1/anti-programmed cell death protein 1 (anti-PD-1), and anti-cytotoxic T-lymphocyte-associated antigen 4]. This evidence is reinforced by numerous *in vitro*, animal, and clinical studies that demonstrate the role of microbial pathways in determining therapeutic responses. The microbiome thus influences oncologic outcomes and is now being used to develop novel, tailored therapeutic methods in cancer treatment. However, if the microbiome is to be successfully translated into next-generation oncologic treatments, a new multimodal model of the onco-microbiome must be developed, incorporating gut microbial cometabolisms of pharmacologic drugs into cancer therapy.[4]

PREBIOTICS, PROBIOTICS, SYNBIOTICS, AND POSTBIOTICS

Prebiotics are non-digestible food fibers produced by gut microorganisms. Prebiotics benefit the gut microbiome by selectively increasing the development and activity of commensal microorganisms such as Lactobacillus and Bifidobacterium, mostly through the generation of SCFAs. Previous research has shown that SCFAs can protect against a variety of diseases by increasing gut epithelial integrity, regulating metabolism, and boosting immunity. Our expertise on prebiotics' positive benefits is confined to their anticancer properties, and we presently have little understanding of how prebiotics influence chemotherapy-induced toxicity, chemosensitivity, or both.[4,5]

The microbiota's anticancer effects: how it influences the growth of T cells that produce IL-9

Transforming growth factor-beta and interleukin (IL)-4 have been known to promote IL-9 secretion in T cells since 1994, but it wasn't until 2008 that IL-9-secreting CD4 T cells (Th9 cells) were identified.[2] Beyond their strong IL-9 release, Th9 cells secrete IL-10 and IL-21 and are extremely pro-inflammatory in the body. Subsequent research has revealed that Th9 cells contribute to antitumor immunity, notably in the context of melanoma. IL-9-producing CD8 T cells, known as Tc9 cells, are potent effector T cells *in vivo*, similar to Th9 cells. Adoptive transfer of IL-9-producing T cells (Th9 or Tc9) into tumor-bearing mice results in cancer eradication *in vivo* via direct anticancer effects and the activation of anticancer immune responses. The importance of these discoveries has been extended to humans, as evidenced by the improved clinical prognosis of cancer patients with high levels of IL-9-producing cell infiltration. The environmental conditions that cause IL-9-producing T cells to be activated *in vivo* are still unknown.[6]

The intratumoral microbiome's function in tumor progression and therapeutic implications

Microbes are present throughout the human body and play important roles in a range of physiological and pathological processes. However, due to various limiting factors such as contamination and low biomass, our current understanding of the intratumoral microbiome remains limited. The intratumoral microbiome supports or inhibits tumor growth by engaging in metabolic activities within the body, altering cancer-related signaling pathways, and impacting host cell function and the immune system. It is important to highlight that the composition and number of intratumoral microorganisms differ greatly between tumor types, which may influence many aspects of tumor genesis, development, and metastasis. These findings suggest that the intratumoral microbiome has tremendous potential as a diagnostic and prognostic indicator. By regulating intratumoral bacteria to harness cancer therapy, chemotherapy or immunotherapy can be made more effective while reducing side effects. The human microbiome refers to all microorganisms, collective genomes, and their metabolites that live in the human body. The human microbiome is made up of billions of microorganisms, including bacteria, fungi, viruses, archaea, and

eukaryotes, with bacteria dominating. Microbial populations thrive throughout the body, including the skin, respiratory system, urogenital system, and digestive system, with the gut serving as bacteria's principal habitat. Furthermore, microorganisms such as bacteria have been discovered in numerous organs previously assumed to be sterile, including the thyroid, pancreas, and liver. The intratumoral microbiota can now be studied more easily using next-generation gene sequencing techniques. The microbiome and the tumor microenvironment (TME) may interact in both directions. The TME's rich nutrition supply, vascular flow, and immunosuppressive milieu may promote bacterial migration and colonization. However, the existence of a tumor can alter normal anatomic architecture, allowing microbial translocation from surrounding organs to the TME. Finally, microorganisms coexist with cancer cells and are incorporated into the tumor microenvironment. Furthermore, the intratumoral microbiome is a component of the tumor microenvironment and has a role in cancer pathophysiology. The microbiome has been shown to affect the efficacy and toxicity of cancer treatments such as chemotherapy, immunotherapy, and radiation. Dietary, probiotic, prebiotic, and fecal microbiota transplants are being investigated as potential therapeutic approaches to improve cancer treatment outcomes.[7]

Experiments show a close relationship between *H. pylori* and the development of atrophic gastritis, metaplasia, dysplasia, and gastric cancer. Its tumorigenic activity is supported by studies demonstrating that eradication of *H. pylori* is a crucial approach for lowering the risk of developing *H. pylori*-driven gastric cancer, including a risk reduction of developing metachronous cancer in patients with endoscopically resected early gastric cancer. Its infection has been linked to the development of gastric cancer through a variety of processes, many of which involve the production of virulence factors (such as CagA and VacA) that cause endoplasmic reticulum stress, autophagy, and oxidative stress in the gastric epithelium. Despite the well-established link between *H. pylori* and stomach cancer, some studies have found an inverse relationship between *H. pylori* and the chance of developing esophageal adenocarcinoma, implying that this bacteria may play a protective role in specific settings. Emerging findings from high-throughput sequencing techniques have revealed non-*H. pylori* stomach microbial populations linked to gastric cancer.[1]

CHEMOTHERAPY TOXICOLOGY

Many cancer treatments are effective on all quickly growing cells except neoplastic cells; therefore, damage can occur in several systems. These poisons can cause death and morbidity, as well as increased costs and treatment disruptions. A recent study reveals that microbiome changes may be linked not just to disease and response but also to toxicity. Major changes in the oral and intestinal microbiota have been associated with serious doxorubicin-induced adverse effects like cardiomyopathy and intestinal mucositis. However, stimulating the bacterial muramyl dipeptide-associated nucleotide-binding and oligomerization domain (NOD)-2 inhibits doxorubicin-induced mucosal injury. The combination of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* probiotics can reduce cisplatin-induced toxicity while enhancing antitumoral activity. Methotrexate-induced intestinal toxicity has been linked to microbial products and endogenous damage-associated molecular patterns-induced TLR4 activation.[8,9]

The intestinal microbiota controls pancreatic beta-cell mass, fat tissue inflammation, and lipid distribution. Cachexia can develop in tumor patients following fat metabolism and adipose tissue abnormalities. Some chemotherapeutics, such as cisplatin, can cause muscle weakness similar to cancer cachexia, and chemotherapy pharmacokinetics may differ in cachectic individuals. Although the mechanisms behind cancer cachexia are not fully understood, it is hypothesized that this illness is intimately tied to intestinal microbiota and energy metabolism and that changes in the microbiota may be responsible for the pathology. Probiotics, either alone or in combination with nutritional support items, may relieve cancer-related cachexia in patients.[8-10] Antibiotics (ATBs) are routinely given to cancer patients undergoing chemotherapy or immunotherapy as a precaution against various infections caused by a reduced immune system.

Our present understanding of the role of specific bacteria species or bacterial functions in therapy responses implies that ATBs could be repurposed and directed against the microbiome as an adjuvant to cancer treatment. This might be accomplished, for example, by selectively eliminating pathogenic bacteria that have a detrimental impact on therapy responses while preserving commensal bacteria that have a positive impact on both the host and drug responses. Furthermore, since bacteria modulate chemoresistance and chemosensitivity via a variety of molecular routes, antibiotics can be employed to decrease bacterial actions that impair drug responses. There is little evidence to suggest that prior antibiotic (pATB) medication influences the efficacy of PD-1 inhibitors in advanced gastric cancer. In contrast, pATB does not affect Irinotecan-treated patients' outcomes. A multivariable analysis of all patients treated with PD-1 inhibitors indicates that anti-tuberculosis treatment is independently associated with poorer progression free survival and overall survival. The administration of pATBs is related to decreased gut microbiome diversity, lower abundance of Lactobacillus gasseri, and disproportional enrichment of circulating exhausted CD8+ T cells, all of which are associated with poor outcomes. Given the lower treatment response and poor survival outcomes of pATB administration followed by PD-1 blocking, ATBs should be recommended with caution in patients with AGC who are scheduled to get PD-1 inhibitors.[4,10]

Radiotherapy and microbiota

Many cancer patients are treated with ionizing radiation. Radiotherapy may cause intestinal cell death as well as changes in microbiota composition. Local radiation causes immunogenic tumor cell death and promotes systemic inflammation and immunity. The impact of microbiota on radiotherapy responsiveness and radiation damage is not fully understood. Ionizing radiation can induce an anticancer response that necessitates immune-related and antigen-presenting dendritic cell and T lymphocyte activation beyond the radiation field, also known as the abscobal effect. Given that the intestinal microbiota increases immunogenic cancer cell death in response to chemotherapy and immunotherapy, it has been proposed that it may also boost the immunostimulatory effect of radiation therapy, hence increasing treatment response.[11,12]

Immunotherapy and microbiota

Many cancer patients have short response times after traditional chemotherapy treatments and resistance to treatment develops over time, leading to tumor recurrences. Long-term response rates have been reached with immunotherapy techniques in studies undertaken in hematological and solid neoplasms, particularly in patients with metastatic lung cancer and melanoma resistant to chemotherapy. However, the efficacy of immunotherapy remains restricted due to the heterogeneity of immune responses among patients and tumor types. Due to the regulatory effects of gut microbiota on the immune response, microorganism-based techniques are expected to enhance the efficacy of immunotherapy. Also, a growing body of evidence suggests that gut microbial dysbiosis is involved in the genesis and progression of colorectal cancer (CRC) via interaction with the host immune system. Given the close link between the gut microbiota and anticancer immune responses, the microbiota is a viable target for modifying immunotherapy responses in preclinical CRC models. However, the postulated mechanisms for how these bacteria influence immune responses and immunotherapy efficacy remain unknown. In this review, we highlight recent results on clinical gut microbial dysbiosis in CRC patients, the reciprocal interactions between gut microbiota and the innate and/or adaptive immune systems, and the impact of gut microbiota on immunotherapy response in CRC. An increased understanding of gut microbiota-immune system interactions will aid in the rational application of microbiota as a clinically promising diagnostic or treatment method in cancer immunotherapy.[12,13]

The role of stem cell application and microbiota

The relationship between cancer and the microbiota has become a significant research topic, focusing on the impact of microbial communities on cancer formation, progression, and treatment outcomes. The gut microbiota regulates immunological responses, metabolism, and inflammatory pathways, crucial in cancer biology. Some microbial species promote tumor growth, while others may have a protective effect. The microbiome can directly influence carcinogenesis by creating genotoxins or indirectly

by directing immune responses and altering the tumor microenvironment. Stem cells, which can differentiate into various cell types and self-renew, are used in regenerative medicine to treat various disorders by replacing damaged cells or tissues. They are useful for tissue repair in spinal cord injury, heart disease, and degenerative disorders, and are critical in cancer treatment with hematopoietic stem cells.[14,15]

Recent research highlights the relationship between stem cells and microbiota. Microbial metabolites influence gut regeneration, while microbiota can influence stem cell development and proliferation, particularly in bone marrow hematopoietic stem cells. Certain microbiota-derived chemicals can reduce inflammation, aiding in stem cell therapy. This combination of stem cell therapy and microbiota regulation could provide new therapeutic routes in regenerative medicine, offering expanded treatment options for chronic diseases, aging, and cancer.[16-18]

NUTRITION AND METABOLISM

The gut microbiota generates a variety of nutrients, including SCFAs, B vitamins, and vitamin K. Multiple metabolic interactions with the human host and each other have a variety of effects on human nutrition and metabolism. Anaerobic gut flora produces butyrate, an essential SCFA. Butyrate-producing bacteria are a promising probiotic candidate for addressing microbial dysbiosis in gastrointestinal conditions like inflammatory bowel diseases (IBD). One example is the clostridial cluster IV strain *Butyricicoccus pullicaecorum 25-3(T)*. Butyrate treatment prevents arthritis and reduces pro-inflammatory cytokine production in mice in collagen-induced arthritis models. Folate is a B-group vitamin that humans cannot synthesize. *Bifidobacteria, Enterococcus faecium*, and *Streptococcus thermophilus (S. thermophilus)* all produce folate in skim milk. Fermentations with a combination of *S. thermophilus* and Bifidobacterium animalis produce a sixfold rise in folate. As a result, milk might be regarded as a component in the gut microbiome's folate production. Furthermore, certain dietary lipids bypass digestion in the small intestine and enter the colon, where the gut microbiota can metabolize them.[19] The intestinal epithelium barrier is one of the most significant interfaces between the environment and the body's internal milieu, and epithelial barrier malfunction can result in inflammatory diseases like IBD. Microsporidia are intracellular fungus infections that cause chronic diarrhea and systemic inflammation. Human disorders have been linked to seven microsporidia taxa: Enterocytozoon, Encephalitozoon, Nosema, Pleistophora, Trachipleistophora, Vittaforma, and Brachiola. The most common microsporidian detected in patients is Enterocytozoon bieneusi. Recently, it was discovered that dengue shock syndrome -induced IBD is more likely to occur in the host when microsporidia are present. Furthermore, microsporidia infection increases epithelial permeability, inhibits wound healing, and degrades the tight junction protein *zonula occludens-1* (ZO-1). This shows that fungi linked with IBD may affect intestinal barrier integrity.[19,20]

Diagnostic tools and management

- *Colonoscopy biopsies*

Colonoscopy for biopsies is the gold standard for diagnosing and monitoring IBD, but it is an intrusive and uncomfortable operation. However, it is important to emphasize that this form of sampling necessitates an invasive endoscopic procedure. Biopsies harm the epithelium and may result in bleeding. As a result of limited mucosal samples in biopsies, sampling bias may develop.[19,21,22]

- *Mucosal brush samples*

When obtaining samples of epithelial-associated bacteria, mucosal brushing is preferred over mucosal biopsy. The brush sample approach is less traumatic on the epithelium, covers a larger surface area, and contains more bacteria-to-host deoxyribonucleic acid (DNA) than a mucosal biopsy. In contrast to biopsy samples, protected specimen brush sampling yields region-specific, uncontaminated samples free of human DNA and high in bacterial DNA. Brush samples have been used in studies to investigate gut microbiota-implicated IBD. This type of sampling may be safer than a biopsy. Surprisingly, net or brush catheters for sample collection also appear. Brush catheters are more likely to capture the inner layer of intestinal mucus, whereas net catheters are more likely to collect the outer layer and intestinal fluid in bigger samples.[19,23]

- *Laser-captured microdissection samples*

Laser capture microdissection (LCM) is an efficient and precise method for separating individual cells or groups of cells of interest from a tissue sample. Compared to traditional microdissection procedures, the use of LCM offers significant advantages. This approach can be used to identify therapeutic interventions, diagnostic biomarkers, and disease precursors.[19,24]

- *Fecal samples*

The gastrointestinal tract (GIT) has a variety of bacterial communities and spans from the mouth to the anus. Recent studies have used stool samples in IBD or GIT disease studies.[19,25-27] Although fecal sampling is a feasible and non-invasive method, it is crucial to choose and use relevant GIT samples for research on gut-related illnesses, as fecal samples do not fully represent the digestive tract's microbiota. A fecal sample makes it difficult to explain the microbiota in other intestinal compartments since the microbiota in the rectum is only similar to that of the colon. In rhesus macaques, the lumen and mucosa of the colon had a substantial relationship with stool content, whereas the distal small intestine had an average correlation. As a result, assessing fecal microbiome study results at the genus and phylotype levels is critical, as the fecal microbiota composition may not be conclusively linked to GIT disorders. The mucosal microbiome differs from the fecal microbiome in terms of representation.[28,29]

In conclusion, according to research, the human microbiota plays an important role in cancer formation, progression, and therapy response. The microbiota can increase cancer risk by modulating the immune system, causing chronic inflammation, and producing chemicals that promote or inhibit tumor growth. Certain microbial species can lead to cancer development in organs such as the gut and liver, whereas a well-balanced and diversified microbiome can boost the immune system's ability to fight malignant cells. The microbiota also influences cancer therapy by regulating medication metabolism and immunological activity, paving the way for microbiome-based interventions such as probiotics, dietary modifications, and fecal microbiota transplants. Understanding the complicated link between cancer and the microbiota provides a potential facility for new cancer prevention, diagnosis, and treatment strategies. Future research may result in personalized and effective cancer treatments, emphasizing the microbiota as a biomarker and target in the battle against cancer.

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REFERENCES

1. Matson V, Chervin CS, Gajewski TF. Cancer and the microbiome-influence of the commensal microbiota on cancer, immune responses, and immunotherapy. Gastroenterology 2021;160:600-13. doi: 10.1053/j.gastro.2020.11.041.
2. Khan AA, Sirsat AT, Singh H, Cash P. Microbiota and cancer: Current understanding and mechanistic implications. Clin Transl Oncol 2022;24:193-202. doi: 10.1007/s12094-021-02690-x.
3. 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.
4. Chrysostomou D, Roberts LA, Marchesi JR, Kinross JM. Gut microbiota modulation of efficacy and toxicity of cancer chemotherapy and immunotherapy. Gastroenterology 2023;164:198-213. doi: 10.1053/j.gastro.2022.10.018.
5. Li HY, Zhou DD, Gan RY, Huang SY, Zhao CN, Shang A, et al. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: A narrative review. Nutrients 2021;13:3211. doi: 10.3390/nu13093211.
6. Apetoh L. Anticancer effects of the microbiota: How the microbiome shapes the development of IL-9-producing T cells. Br J Cancer 2020;123:497-8. doi: 10.1038/s41416-020-0936-1.
7. Meng YF, Fan ZY, Zhou B, Zhan HX. Role of the intratumoral microbiome in tumor progression and therapeutics implications. Biochim Biophys Acta Rev Cancer 2023;1878:189014. doi: 10.1016/j.bbcan.2023.189014.

8. Kunika, Frey N, Rangrez AY. Exploring the involvement of gut microbiota in cancer therapy-induced cardiotoxicity. Int J Mol Sci 2023;24:7261. doi: 10.3390/ijms24087261.
9. Zhao LY, Mei JX, Yu G, Lei L, Zhang WH, Liu K, et al. Role of the gut microbiota in anticancer therapy: From molecular mechanisms to clinical applications. Signal Transduct Target Ther 2023;8:201. doi: 10.1038/s41392-023-01406-7.
10. Kim CG, Koh JY, Shin SJ, Shin JH, Hong M, Chung HC, et al. Prior antibiotic administration disrupts anti-PD-1 responses in advanced gastric cancer by altering the gut microbiome and systemic immune response. Cell Rep Med 2023;4:101251. doi: 10.1016/j.xcrm.2023.101251.
11. Al-Qadami G, Van Sebille Y, Le H, Bowen J. Gut microbiota: Implications for radiotherapy response and radiotherapy-induced mucositis. Expert Rev Gastroenterol Hepatol 2019;13:485-96. doi: 10.1080/17474124.2019.1595586.
12. Genc AC, Hacıbekiroğlu İ. Microbiata and cancer. Journal of BSHR 2017;1(Special Issue):123-131.
13. Hou X, Zheng Z, Wei J, Zhao L. Effects of gut microbiota on immune responses and immunotherapy in colorectal cancer. Front Immunol 2022;13:1030745. doi: 10.3389/fimmu.2022.1030745.
14. Weissman IL. Stem cells: Units of development, units of regeneration, and units in evolution. Cell 2000;100:157-68. doi: 10.1016/s0092-8674(00)81692-x.
15. Daley GQ, Scadden DT. Prospects for stem cell-based therapy. Cell 2008;132:544-8. doi: 10.1016/j.cell.2008.02.009.
16. Dheer R, Young VB. Stem-cell-derived models: Tools for studying role of microbiota in intestinal homeostasis and disease. Curr Opin Gastroenterol 2021;37:15-22. doi: 10.1097/MOG.0000000000000691.
17. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr 2011;94:58-65. doi: 10.3945/ajcn.110.010132.
18. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012;336:1268-73. doi: 10.1126/science.1223490.
19. Wang X, Peng J, Cai P, Xia Y, Yi C, Shang A, et al. The emerging role of the gut microbiota and its application in inflammatory bowel disease. Biomed Pharmacother 2024;179:117302. doi: 10.1016/j.biopha.2024.117302.
20. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue Barriers 2017;5:e1373208. doi: 10.1080/21688370.2017.1373208.
21. Macrae FA, Bhathal PS. Colonoscopy and biopsy. Baillieres Clin Gastroenterol 1997;11:65-82. doi: 10.1016/s0950-3528(97)90054-3.
22. Kudo SE, Misawa M. Progress in magnifying colonoscopy: Road to optical biopsy. Dig Endosc 2022;34 Suppl 2:91-4. doi: 10.1111/den.14141.
23. Matsumoto H, Kuroki Y, Higashi S, Goda K, Fukushima S, Katsumoto R, et al. Analysis of the colonic Mucosa Associated Microbiota (MAM) using brushing samples during colonic endoscopic procedures. J Clin Biochem Nutr 2019;65:132-7. doi: 10.3164/jcbn.19-3.
24. Funke B. Laser microdissection of intestinal epithelial cells and downstream analysis. Methods Mol Biol 2011;755:189-96. doi: 10.1007/978-1-61779-163-5_15.
25. Minkoff NZ, Aslam S, Medina M, Tanner-Smith EE, Zackular JP, Acra S, et al. Fecal microbiota transplantation for the treatment of recurrent clostridioides difficile (Clostridium difficile). Cochrane Database Syst Rev 2023;4:CD013871. doi: 10.1002/14651858.CD013871.pub2.
26. Kim HK, Kostidis S, Choi YH. NMR Analysis of fecal samples. Methods Mol Biol 2018;1730:317-28. doi: 10.1007/978-1-4939-7592-1_24.
27. Tarallo S, Ferrero G, Gallo G, Francavilla A, Clerico G, Realis Luc A, et al. Altered fecal small RNA profiles in colorectal cancer reflect gut microbiome composition in stool samples. mSystems 2019;4:e00289-19. doi: 10.1128/mSystems.00289-19.
28. Abdelbary MMH, Hatting M, Bott A, Dahlhausen A, Keller D, Trautwein C, et al. The oral-gut axis: Salivary and fecal microbiome dysbiosis in patients with inflammatory bowel disease. Front Cell Infect Microbiol 2022;12:1010853. doi: 10.3389/fcimb.2022.1010853.
29. Han A, Yang M, Chen B, Cao G, Xu J, Meng T, et al. Microbiome and its relevance to indigenous inflammatory bowel diseases in China. Gene 2024;909:148257. doi: 10.1016/j.gene.2024.148257.