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The role of gut microbiota in digestive system cancers: mechanisms and potential therapeutic targets

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Abstract. The rising prevalence of digestive system cancers—including colorectal, stomach, esophageal, and pancreatic cancers—poses significant global health challenges, exacerbated by the elusive early-stage symptoms that lead to late-stage diagnoses with poor prognoses. Emerging evidence suggests a substantial role of gut microbiota in the pathogenesis of these malignancies. This paper reviews the complex interactions between the gut microbiota and the host, particularly focusing on dysbiosis and its contributions to carcinogenesis through mechanisms like chronic inflammation, immune response alterations, and carcinogenic metabolite production. Epidemiological data highlight the incidence and mortality rates associated with these cancers, emphasizing the influence of lifestyle, environmental factors, and genetics, with a newfound focus on microbial compositions. The gut microbiota's role extends from influencing metabolic profiles to impacting regulatory T-cell functions and inflammatory pathways, which are pivotal in tumor progression. Specific bacteria such as Clostridium nucleatum and Helicobacter pylori are scrutinized for their direct associations with colorectal and stomach cancers, respectively. Furthermore, the review discusses potential therapeutic interventions targeting microbial dysbiosis, such as dietary modifications, probiotics, and microbiota-targeted therapies, which could revolutionize treatment paradigms. This comprehensive analysis aims to underscore the gut microbiota as a critical factor in digestive system oncology, providing insights into future research directions and novel therapeutic strategies

Keywords: Cancer, intestinal flora, microorganism, microenvironment, digestive system.

1. Introduction

In today's society, the richness of the human diet has led to cancers of the digestive system—specifically colorectal, stomach, esophageal, and pancreatic cancers—becoming a major global health problem [1]. These cancers are often aggressive and tend to exhibit hidden symptoms in the early stages, making them easy for patients to overlook; however, the prognosis is poor when they are diagnosed at later stages. Understanding the multifactorial etiology of these malignancies is critical to advancing prevention and treatment strategies. The importance of gut microbiota to human health has been the subject of recent research, and mounting data suggests that microbial dysbiosis may be a major component in the development of malignancies of the digestive system.

One of the most prevalent malignancies worldwide, particularly in affluent nations, colorectal cancer claims the lives of over 900,000 people year and accounts for close to 2 million new cases. [2]. Stomach

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cancer is particularly common in East Asia due to differences in dietary habits, while esophageal cancer is more prevalent in regions such as East Africa and Central Asia. Pancreatic cancer, while relatively rare, is one of the deadliest cancers, with a five-year survival rate of less than 10 percent. Scientific research has shown that environmental factors, lifestyle choices, and genetics play an important role in the pathogenesis of these cancers, but the importance of gut microbiota is beginning to come into view as research goes deeper.

The gut microbiota is made up of trillions of microorganisms, including bacteria, fungi, and viruses, that colonize the gastrointestinal tract. In healthy individuals, this microbial community is symbiotic with the host, contributing to nutrient absorption, vitamin production, immune regulation, and maintenance of the intestinal barrier. On the other hand, external stressors have the ability to alter the gut microbiota and cause dysbiosis, which has been connected to a number of illnesses, including as cancer, autoimmune diseases, and metabolic disorders.

2. Composition and Function of Intestinal Flora

The gut flora varies along the length of the digestive tract, with different microbes inhabiting different parts of the digestive system, with the colon being the most densely populated and containing the most microbial species. The dominant flora includes Firmicutes and Bacteroidetes, but Proteobacteria, actinobacteria and Clostridium are less numerous. The stability and diversity of these flora are crucial for preserving the gut's delicate balance of homeostasis. However, it is important to recognize that certain external factors, including nutrition, antibiotic use, infections, and chronic illnesses, can upset this delicate balance and increase the risk of developing a number of illnesses, including cancer. The makeup of the gut microbiota is influenced by a number of variables, including genetics, medication, environment, and food. One of the most important variables is nutrition; a plant-based, high-fiber diet encourages a diverse and healthy microbiome that improves the ecological balance of the gut microbiota, while a high-fat, low-fiber diet may encourage the growth of pro-inflammatory bacteria that cause inflammation. [3]. Antibiotics, while essential for treating infections, can also eliminate beneficial bacteria in the gut, leading to long-term effects on the microbiome. This reduction in microbial diversity allows disease-causing species to dominate.

3. Relationship between intestinal flora and digestive system cancers

An increasing body of research indicates that the gut microbiota has a role in the onset and progression of digestive system cancer [4]. Dysbiosis can cause the generation of carcinogenic compounds, modify immunological responses, and encourage chronic inflammation. Furthermore, a few species of bacteria have been connected to particular kinds of cancer. For instance, Helicobacter pylori is known to cause stomach cancer, whereas Clostridium nucleatum has been connected to colorectal cancer.

3.1. Colon cancer

Studies have shown that colorectal cancer patients have significant differences in their gut microbiota compared to healthy individuals [5]. In patients with colorectal cancer, there is often an excess of pro-inflammatory and potentially carcinogenic bacteria, such as Clostridium nuclear and E. coli. At the same time, beneficial bacteria such as Lactobacillus and bifidobacterium, which contribute to intestinal barrier function and anti-inflammatory processes, are reduced, thus altering the ecology of the gastrointestinal tract.

One of the key mechanisms by which the gut microbiota leads to colorectal cancer is through chronic inflammation. For example, Clostridium nucleae can accelerate tumor cell production by activating inflammatory pathways such as NF-κB, resulting in increased cell proliferation and decreased apoptosis [6]. In addition, bacterial metabolites such as secondary bile acids and toxins produced by pathogenic strains of E, as well as E. coli, can damage DNA, and cell DNA is damaged, thus contributing to cancer.

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3.2. Gastric cancer

Gastric cancer is known to be caused by Helicobacter pylori infection, particularly in those who have the infection on a continuous basis. This bacteria has the ability to cause long-term inflammation of the stomach mucosa, which can result in intestinal gastric mucosa metaplasia, atrophic gastritis, and ultimately cancer. This carcinogenic process is thought to be driven by a combination of bacterial virulence factors, such as CagA, and host immune responses.

Changes in the stomach flora may contribute to stomach cancer development in addition to H. pylori [7]. Research has shown that patients with gastric cancer have altered stomach microbiomes, with an increase in harmful bacteria including Weissella and Prevotella and a decrease in microbial diversity. These changes may contribute to an environment conducive to cancer development through mechanisms such as inflammation and oxidative stress.

3.3. Oesophageal cancer

Esophageal cancer, especially esophageal adenocarcinoma, is associated with changes in the esophageal microbiota. Patients with Barrett's esophagus, a precursor to esophageal cancer, often exhibit microbial dysbiosis, characterized by a shift from gram-positive to gram-negative bacteria. This shift is thought to promote a pro-inflammatory environment, which can lead to the development of cancer. In particular, porphyromonas and tannin bacteria are associated with the occurrence of esophageal cancer.

3.4. Pancreatic cancer

One of the deadliest tumors, pancreatic cancer has a dismal prognosis and few available treatments. There is growing evidence indicating that pancreatic cancer growth and progression may be influenced by the gut bacteria. Pancreatic cancer has been associated with dysbiosis in the gut and oral microbiota, as well as an elevated risk of the disease in relation to specific bacteria such actinomycetes aggregates and Porphyromonas gingivalis.

4. Mechanisms of intestinal flora and digestive system cancer

Investigations are ongoing to determine the processes by which gut microbes affect pancreatic cancer. Bacteria from the gut may migrate to the pancreas, where they may cause inflammation and encourage the growth of tumors. This is one probable route. Furthermore, microbial metabolites that modify the immune system and foster an inflammatory milieu, like secondary bile acids and short-chain fatty acids (SCFAs), may have an impact on the course of pancreatic cancer development. [8].

The gut microbiota plays a vital role in regulating the immune system, both locally and throughout the body. Certain bacteria can stimulate the production of regulatory T cells (Tregs), which help maintain immune homeostasis and prevent excessive inflammation. However, in the context of cancer, dysbiosis can upset this balance, leading to chronic inflammation and suppression of anti-tumor immune responses. For example, Bacteroides fragilis has been shown to induce the production of pro-inflammatory cytokines that promote the development of tumors.

Chronic inflammation is a recognized risk factor for many cancers, including those of the digestive system. The gut microbiota can promote inflammation by producing pro-inflammatory molecules such as lipopolysaccharides (LPS) and bacterial toxins. These molecules can activate immune cells, leading to the release of inflammatory cytokines and chemokines, which promote cell proliferation, angiogenesis, and tumor growth. In colorectal cancer, for example, inflammation driven by dysbiosis has been shown to promote tumor progression by activating the NF-κB and STAT3 signaling pathways.

Microbial metabolites, such as short-chain fatty acids, secondary bile acids and polyamines, exert a significant role in cancer development. Short-chain fatty acids, especially butyrate, have been shown to have anti-inflammatory and anticancer effects by promoting cancer cell apoptosis and inhibiting cell proliferation. However, certain bacterial metabolites, such as secondary bile acids, have been implicated in promoting carcinogenesis, particularly in the colon. These metabolites can cause DNA damage, promote oxidative stress, and activate pro-tumor signaling pathways.

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There is growing evidence that the gut microbiota can interact with host genes to influence cancer development. For example, certain bacterial species have been shown to regulate the expression of genes involved in immune response, inflammation, and cell proliferation. In addition, host genetic factors can influence the composition of the gut microbiota, creating complex interactions between genetic and microbial factors in cancer development.

5. Clinical studies and case studies

Several clinical studies have investigated the role of the gut microbiota in cancers of the digestive system. For example, a study by Feng et al. showed that colorectal cancer patients exhibited different microbial signatures compared to healthy controls, with an overrepresentation of C. nuclealis * and E. coli *. Similarly, other studies have shown alterations in gastric microbiota in patients with stomach cancer, characterized by reduced microbial diversity and an increase in pathogenic species [9].

Clinical data suggest a close relationship between microbial imbalance and the occurrence of digestive system cancers. However, it is unclear whether these microbial changes are a cause or a result of the cancerous state. For example, while the presence of specific bacteria such as Clostridium nucleatum has been linked to colorectal cancer, whether these bacteria drive tumorgenesis or simply thrive in an altered tumor environment is still a controversial topic. Similarly, in stomach cancer, Helicobacter pylori is a recognized cause, but the role of other microorganisms in the tumor microenvironment and their potential contribution to cancer progression needs to be further explored.

In esophageal and pancreatic cancer, clinical data are more limited, but emerging evidence suggests that microbial dysbiosis may be an important factor. The composition of the oral and esophageal microbiota has been shown to differ in patients with esophageal adenocarcinoma, while changes in the gut microbiota have been linked to pancreatic cancer. Further clinical trials are needed to establish causation and identify potential microbial biomarkers for early detection of these cancers.

6. Treatment and prevention

One of the key ways to mitigate the role of dysbiosis in cancer development is by restoring a healthy gut microbiome. Probiotics, prebiotics, and dietary modifications are among the most widely studied strategies [10]. Probiotics, which are living microbes with health benefits when consumed in adequate amounts, have shown promise in improving gut health and reducing inflammation. For example, the intake of probiotics such as Lactobacillus and Bifidobacterium has been linked to decreased inflammation and enhanced gut barrier function, potentially reducing cancer risk.

Prebiotics, which are indigestible fibers that promote the growth of beneficial bacteria, represent another effective strategy [10]. A diet rich in prebiotic fibers such as inulin and fructooligosaccharides can promote the growth of beneficial bacteria and produce anti-inflammatory short-chain fatty acids such as butyrate. Increasing fiber intake through dietary adjustments may lower the risk of colorectal cancer. Similarly, a plant-based diet rich in fruits, vegetables, and whole grains can promote microbial diversity and contribute to a healthy gut environment.

Recent research suggests that the gut microbiota may play a key role in the effectiveness of cancer treatments, particularly immunotherapy [10]. For example, the success of immune checkpoint inhibitors in treating cancers such as melanoma has been linked to the composition of the gut microbiota. Patients with a more diverse microbiome or higher levels of certain beneficial bacteria responded better to immunotherapy. In this case, regulating the gut microbiota through diet, probiotics, or fecal microbiota transplantation (FMT) may improve the efficacy of cancer treatments.

FMT, which involves transplanting stool from a healthy donor into a patient's gastrointestinal tract, has demonstrated promise in restoring microbial diversity and improving immune responses in cancer patients [10]. Although still in the early stages of research, FMT has been studied in clinical trials as an adjunct treatment for diseases such as colorectal cancer. Further research is needed to determine the safety and effectiveness of this approach in wider cancer treatment applications.

Ongoing research aims to elucidate the complex relationship between gut microbiota and cancer development while exploring new therapeutic avenues. One area of interest is the identification of

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specific microbial signatures that could serve as biomarkers for early cancer detection. For example, the presence of C. nucleatum in stool samples is considered a potential non-invasive biomarker for colorectal cancer.

In addition, there is growing interest in developing microbiome-targeted therapies, such as using designer probiotics or phages to selectively target cancer-associated pathogenic bacteria. Another promising avenue of research involves exploring how microbial metabolites, such as short-chain fatty acids and bile acids, can be used to prevent or treat cancer. By understanding the metabolic pathways by which these compounds influence cancer development, the researchers hope to develop novel therapeutic strategies that target microbial metabolism.

Finally, integrating microbiome research into precision medicine holds great potential in the future. By analyzing the unique microbial characteristics of individual patients, personalized treatments can be developed that target specific microbial imbalances. This approach could lead to more effective cancer prevention strategies and improve patient outcomes by tailoring treatments to a patient's microbiome.

7. Conclusion

In summary, gut flora plays a crucial role in the occurrence and development of digestive system cancers. Dysbiosis, characterized by an imbalance between beneficial and harmful flora, has been associated with colorectal, gastric, esophageal, and pancreatic cancers. Microbial dysbiosis promotes cancer through multiple mechanisms, including chronic inflammation, immune regulation, and the production of carcinogenic metabolites. Specific bacterial species, such as Clostridium nucleatum and Helicobacter pylori, were identified as key players in colorectal and gastric cancers, respectively. A growing body of evidence supports the role of the gut microbiota in cancer, highlighting the potential of microbiota-targeted therapies. Interventions aimed at restoring healthy gut microbiota, such as the use of probiotics, prebiotics, and FMT, are promising strategies for preventing and treating cancer. It should be added that the potential to enhance the efficacy of cancer treatments through microbiome regulation opens new avenues for research and clinical applications.

While the findings are encouraging, some limitations must be acknowledged. First, much of the evidence linking the gut microbiota to cancer is correlational, and establishing causality remains challenging. Further research is needed to elucidate the exact mechanisms by which dysbiosis leads to cancer and to determine whether restoring a healthy microbiome can prevent or reverse cancer progression. However, the gut microbiome is highly complex and personalized, making it difficult to develop universal treatments. Factors such as genetics, diet, environment, and lifestyle all influence the composition of the microbiome, and these variables must be considered when designing treatments that target the microbiome. While probiotics and prebiotics have shown promise in preclinical studies, their efficacy in clinical settings remains to be conclusively proven.

Future research should focus on large-scale longitudinal studies to better understand the temporal relationship between dysbiosis and cancer development. Investigating the microbiome profiles of high-risk individuals over time can provide insights into early microbiome changes before cancer develops, and clinical trials are also needed to evaluate the effectiveness of treatments targeting the microbiome, including probiotics, prebiotics, and MFTS, in cancer prevention and treatment.

Future research should expand the study of the role of microbial metabolites in cancer. By understanding how microbial metabolism affects carcinogenesis, researchers may discover new therapeutic targets for preventing and treating cancers of the digestive system. Finally, integrating microbiome research into precision oncology could lead to personalized approaches to cancer treatment, improving patient outcomes and advancing the field of cancer treatment.

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