International Journal of Clinical and Experimental Medicine Research, 2024, 8(1), 180-186
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Advances in the Influence of Intestinal Flora on Tumour Development

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How to cite this paper: Cong Li, Nan Zhang, Xiang Li, Yu Li, Xiaojuan Jin, Bin Liang. (2024) Advances in the Influence of Intestinal Flora on Tumour Development. *International Journal of Clinical and Experimental Medicine Research*, 8(1), 180-186.
DOI: 10.26855/ijcemr.2024.01.031

Received: January 17, 2024
Accepted: February 14, 2024
Published: March 12, 2024

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Abstract

Intestinal flora, as an important microenvironment in the human body, is closely linked to tumour development. In this paper, the influence of intestinal flora on tumour development is discussed in depth, aiming to provide a basis for understanding the mechanisms of tumour occurrence and development as well as finding new tumour therapies. Intestinal flora affects tumour development through a variety of mechanisms, including immune regulation, the action of metabolites, and direct stimulation of tumour cells. Different species and numbers of bacteria in the intestinal flora have different effects on tumour development, with beneficial, conditionally pathogenic, and pathogenic flora all having an impact on human tumours. In addition, metabolites and carcinogens of intestinal flora are also closely related to tumour development. This paper reviews the pro- and oncogenic relationships between intestinal flora and tumours, as well as some of the currently known mechanisms by which intestinal flora influence tumour development. The study of the influence of intestinal flora on tumour development is of great significance for an in-depth understanding of the mechanisms of tumour genesis and development, as well as the search for new tumour therapies.

Keywords

Intestinal flora, Tumour, Immune regulation, Metabolites, Carcinogens, Cancer therapy

1. Introduction

As the largest and most complex microbial ecosystem in the human body, the intestinal flora is closely linked to human health and disease development. The intestinal flora, which is known as the second largest genome in human beings, accounts for more than 99 per cent of the microorganisms in the human digestive tract, with about 1,000-1,150 species. In recent years, more and more studies have shown that gut flora plays an important role in tumour development. Gut flora affects tumour development through a variety of mechanisms, including immune modulation, action of metabolites and direct stimulation of tumour cells. The current state of research on the use of microbiota in cancer therapy can be used to better prevent and treat cancer [1]. The aim of this paper is to provide a comprehensive review of the pro-cancer and anti-cancer relationships between intestinal flora and tumours and some of the currently known mechanisms by which intestinal flora affect tumour development, and to explore in depth the influence of intestinal flora on tumour development, which is of great significance for understanding the mechanisms of tumour occurrence and development, as well as for searching for new tumour therapeutic approaches.

2. Interrelationship between intestinal flora and tumours

The current level of research has been able to demonstrate the relevance of the gut flora to tumour immunotherapy,

that immune efficacy can be enhanced by modulation of the gut flora, and that the microbiome has enormous potential in cancer diagnosis and prognosis. Current preclinical and clinical studies are accumulating, confirming that the gut and tumour microbiomes have a significant impact on the efficacy of anti-tumour therapy and the occurrence of adverse effects. Microorganisms inhabiting tumours are an important part of the tumour microenvironment and influence tumourigenesis and progression [2].

The intestinal flora is usually divided into three types: beneficial flora, conditionally pathogenic flora and pathogenic flora. Beneficial flora include Bifidobacterium, Lactobacillus acidophilus, Lactobacillus, etc., which can promote intestinal peristalsis, play a role in digesting food, help excretion, etc., and can prevent intestinal infections and improve immunity if the proportion of beneficial flora in the intestinal tract is high. Take Bifidobacterium bifidum as an example, changes in intestinal Bifidobacterium levels or species composition are usually present in cases of intestinal flora dysbiosis. Studies have shown that Bifidobacterium strains can improve symptoms of irritable bowel disease, irritable bowel syndrome, diarrhoea, and allergies. Variations of bifidobacteria in the gut can be observed in many different diseases including immune disorders, inflammatory diseases or cancer. Modulation of the intestinal bifidobacterial population is often considered a target for dietary intervention, providing a rationale for the use of microorganisms of the genus Bifidobacterium as probiotics [3].

Conditionally pathogenic flora include enterococci, Escherichia coli, and Aspergillus, etc. With a high level of beneficial flora in the intestinal tract, conditionally pathogenic flora are usually able to coexist stably with the beneficial flora. If the beneficial intestinal flora is destroyed by improper diet and decreased resistance, the conditionally pathogenic flora may lead to intestinal diseases, such as enteritis, with symptoms such as diarrhoea and abdominal pain. Gram-negative Escherichia coli, the parthenogenetic anaerobic bacterium with the largest human gut microbial population, is also considered a highly versatile species. E. coli exemplifies a multifunctional bacterial species consisting of harmless commensal bacteria and different pathogenic variants capable of causing intestinal or extraintestinal diseases in humans and many animal hosts. Leimbach A et al. cite three insights demonstrated through the comparative phylogenetic, genetic, and phenotypic characterisation of commensal E. coli and pathogenic E. coli to show that the line between extraintestinal virulence and intestinal competitiveness can be blurred, as increased fitness and competitiveness may promote intestinal colonisation as well as extraintestinal infection of E. coli [4]. Based on its "tumour-discovering" nature, E. coli is a programmable delivery vector that can be designed to carry multiple genes for therapeutic or diagnostic cancer drugs.[5]

Pathogenic flora includes Salmonella, Staphylococcus, Pseudomonas aeruginosa, etc. Often improper diet and long-term application of medications may lead to the entry of pathogenic flora into the intestinal tract and cause intestinal disorders, resulting in food poisoning, dyspepsia, malnutrition, and other conditions. Wong SH et al. found that the proportion of highly heterogeneous hyperplasia and polyposis was significantly higher in regular mice fed with fecal samples from CRC patients and healthy individuals compared to controls ($p < 0.05$). Conventional mice fed with CRC patients' faeces developed significantly higher rates of highly heterogeneous hyperplasia ($P < 0.05$) and polyps of the flesh ($P < 0.01$) compared to control faeces. Wong SH et al. further demonstrated that faecal microbiota from colorectal cancer patients can promote tumourigenesis in germ-free mice and mice given carcinogens [6]. Therefore, microbial communities present in the tumour microenvironment promote or inhibit the development of malignant tumours through different mechanisms.

In summary, the variation of Bifidobacterium intestinalis, the three types of intestinal flora - beneficial, conditionally pathogenic and pathogenic—can be observed in many different diseases, and all three types of flora have an impact in human tumours, which further proves that there is a close connection between the changes in the number and types of intestinal flora and the changes in the development of human tumours.

3. Mechanisms of intestinal flora on tumour development

3.1 Metabolites and carcinogen production

The gut microbiome plays a crucial role in the development of colorectal cancer by disrupting the homeostasis of the microenvironment and altering the immune response, as well as the biofilms and toxic metabolites of gut bacteria [7]. Determining the composition of the intestinal flora may provide a diagnostic basis for evaluating the development of colorectal cancer, especially in its early stages. Identifying changes in intestinal bacteria and faecal metabolites may be a non-invasive method of disease detection and lead to strategies to inhibit the growth of colon cancer-associated bacteria and reduce the risk of developing colorectal cancer.

Fermentation of carbohydrates typically produces short-chain fatty acids for use by the host, while protein hydrolysis fermentation also produces phenols, cresols, ammonia and sulphides, which are usually considered to be toxins.

However, the production of specific secondary metabolites with pro- and/or anticarcinogenic activity, such as enterotoxins, cyclic regulators, B vitamins, urolithins, the estrogen estradiol, and mammalian lignans, may be dependent on the abundance of certain strains or functional groups of bacteria [8]. Carcinogens include nitrosamines and phenols, which are capable of inducing cellular mutations through a variety of mechanisms, thereby increasing the risk of cancer. Increased production of phenolic compounds, amines, ammonia, and hydrogen sulphide. These metabolites can be used as a source of nitrogen for bacterial cross-feeding, or they can be absorbed by colonic cells and transported into the bloodstream [9], and their accumulation in the lumen of the colon is associated with increased epithelial cell toxicity [10, 11]. In contrast to potentially harmful gut microbes, gut flora has shown positive anti-tumour effects in immunotherapy and chemotherapy. Furthermore, a healthy diet, avoidance of unnecessary broad-spectrum antibiotics, use of probiotics and prebiotics, and faecal bacterial transplantation to modulate the gut microbiota [12, 13] may be potential ways to reduce the risk of colorectal cancer and may lead to new therapeutic options. In the future, monitoring changes in gut microbes may allow early disease detection and intervention and lead to the development of disease prevention methods Gut bacteria produce carcinogens that can act directly on tumour cells, promoting their proliferation and spread.

3.2 Immune system regulation

The gut microbiota (GM) is the totality of commensal, symbiotic, and pathogenic microorganisms living in our gut [14]. GM-host interactions contribute to the maturation of the host immune system and modulate its systemic response. Some gut bacteria stimulate the maturation and function of dendritic cells, increasing their ability to present tumour antigens and thus enhancing the anti-tumour immune response. Some other types of cancer can also be caused by specific bacterial pathogens, e.g., Salmonella enterica infection can lead to gallbladder cancer. Adaptive immune response activity to specific pathogen infections can lead to the development of mucosa-associated lymphoid tissue-type lymphomas. Meanwhile, H. pylori is capable of a specific immune response and the expression of its antigen-specific T helper cells is the main symptom of gastric mucosa-associated lymphoid tissue lymphoma. Gastric cancer is a disease in which cancer is triggered by bacterial promotion, and H. pylori is considered to be the culprit of gastric cancer. Although H. pylori has been classified as a class I carcinogen, however, gastric cancer requires a complex microbial community for its development [15]. Studies have shown that the incidence of spontaneous atrophic gastritis and gastrointestinal intraepithelial neoplasia in transgenic mice with hypergastrinemia was 80% 6 months after H. pylori infection; however, in the absence of gastrointestinal microbial colonisation, H. pylori infection in this mouse resulted in attenuated gastritis and delayed intraepithelial neoplasia [16]. Gastric atrophy and low gastric acid promoted by H. pylori lead to the overgrowth of microorganisms in the stomach, and overgrowth of microorganisms will lead to greater conversion of dietary nitrogen derivatives to carcinogens; however, it reduces the risk of oesophageal cancer in humans, and the tissue specificity of the bacterial flora has a definite anticancer effect. Gut flora also plays an important role in colorectal cancer (CRC) progression. The effect of tissue-resident commensal bacteria on immunosurveillance in CRC is still poorly understood. Xusheng Z concluded from an experiment analysing intratissue bacteria from colon tissues of patients with CRC that intra-tissue Ruminal Gastrococcus (Rg) and Bradyrhizobium (Bp) degraded lysoglycerophospholipids, which inhibit the activity of and maintain the immunosurveillance function of CD8 T-cells. Lysoglycerophospholipids alone promoted tumour growth, whereas Rg and Bp injections abolished tumour growth. Overall, intra-tissue Lachnospira family bacteria promoted CD8 T cell immunosurveillance and controlled colorectal cancer progression [17].

In summary, the link between the gut microbiota and tumour development is a complex and multifaceted area. These microorganisms influence tumour development through their interactions with the host, modulating the maturation of the immune system and systemic responses. Some gut bacteria are able to stimulate the maturation and function of dendritic cells and increase their ability to present tumour antigens, thereby enhancing the anti-tumour immune response.

3.3 Chronic inflammation

Chronic inflammation is a key factor in tumourigenesis and tumour progression, promoting the development of a pro-cancer microenvironment that sustains cancer progression. Ongoing chronic inflammation in the gut increases the probability of cellular mutations and thus increases cancer risk. Dysregulated intestinal mucosal immunity contributes to the inflammatory signature of systemic inflammation. Gut mucosal immunity is constantly stimulated by pathogenic intestinal commensals, repeated dietary antigens and unhealthy lifestyles, leaving local and systemic inflammation unresolved [18]. Gut ecological dysregulation and microbiota-derived metabolites can trigger brain

inflammation [19]. Multiple mediators and cytokines produced during inflammation can promote tumour cell growth, invasion and metastasis. Inflammatory mediators function like genetic mutagens, disrupting DNA repair mechanisms and cell cycle checkpoints, leading to the accumulation of chromosomal aberrations, which are the main causative factors of cancer [20]. Chronic inflammation is an important intrinsic factor that induces multiple responses, including DNA damage; production of reactive oxygen species and reactive nitrogen species; modulation of malignant degeneration of intestinal epithelial cells (IEC); polarisation and establishment of the tumour microenvironment; activation of transcription factors (e.g., nuclear factor-κB) and IEC non-specific factors (e.g., signalling and activator of transcription factor 3 (STAT3)); and promotion of anti-super-antigen immunity. In the context of unfolded protein response (UPR) activation in epithelial cells, STAT3 activation is involved in tumourigenesis through inflammation-independent mechanisms [21].

In summary, an imbalance of gut flora can lead to chronic inflammation and promote tumour development. Gut bacteria can cause intestinal mucosal damage and inflammatory responses, stimulating cell proliferation, mutation and growth factor release, increasing tumour risk. Harmful substances such as toxins and chemical carcinogens can also affect intestinal cells and immune system function, increasing tumour risk. Therefore, maintaining a balanced and diverse intestinal flora can help prevent chronic inflammation and tumour development.

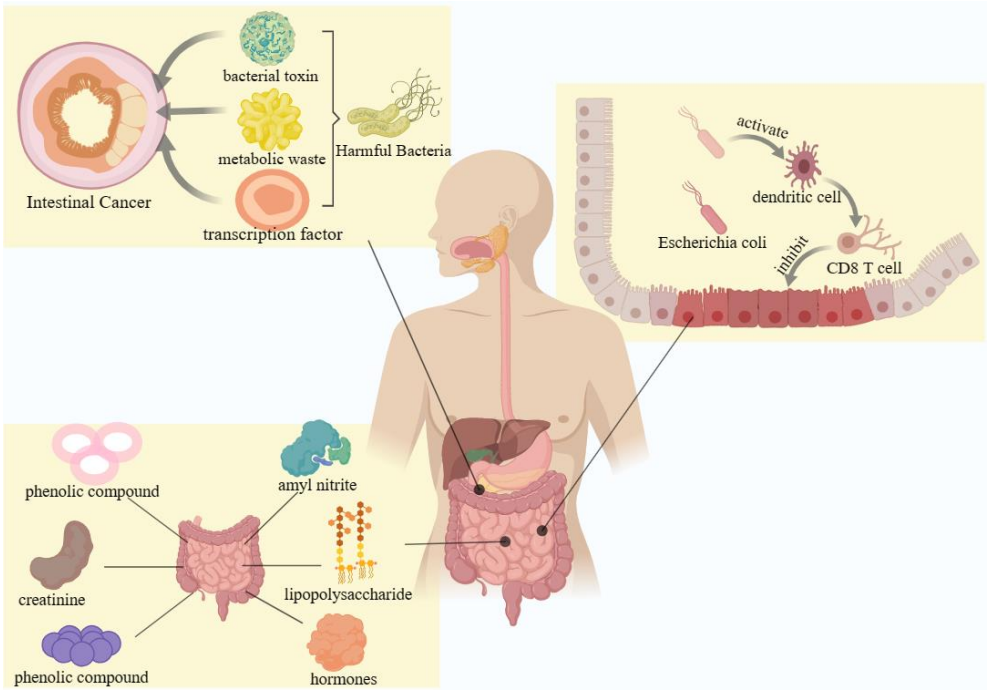

Figure 1. Gut microbes on mechanisms of tumour development.

4. Gut flora on cancer development

4.1 Carcinogenic effects

Gut bacteria can promote tumour development through a variety of mechanisms. These include the production of oncogenic metabolites, induction of chronic inflammation and modulation of immune responses. The main mechanism is that intestinal flora causes mucosal damage and chronic inflammation, which in turn produces harmful substances that cause tumour development and progression. It has been found that the common bacterium Helicobacter pylori activates the inflammatory response and destroys the mucus layer, thus creating an environment that supports tumour growth; in addition, some of the same types of bacteria directly induce intestinal cancer, e.g., the increase of Bacteroidetes-like organisms in the intestine has an oncogenic effect; and colorectal cancers are characterised by hereditary and epigenetic alterations as well as by an infiltration of inflammatory cells between the malignant and mesenchymal cells. However, this infiltration may be influenced by the microenvironment, which in turn affects tumour proliferation, survival, and metastasis as well as tumourigenesis. In particular, metabolites in the cancer microenvironment can stimulate inflammatory cells to induce a chronic inflammatory response, which may lead to colorectal carcinogenesis [22]; some intestinal bacteria are capable of producing carcinogens such as nitrosamines,

which promote the proliferation and spread of tumour cells, and if the intestinal flora is capable of producing cancer-causing nitrosamines from amines and nitrites in vivo, then aerobic bacteria in the faeces may play an important role in providing amine substrates for nitrosation [23]. At the same time, chronic inflammation in the gut can increase the probability of cellular mutations, thereby increasing the risk of cancer. The study shows that genome-wide transcriptome profiling of single cells from normal colorectal tissue (NC), colorectal adenomas (CRAs), and carcinomas was investigated. A potential relationship between disruption of metabolic homeostasis, characterised by activation of the urea cycle (UC), and progression of colorectal tumourigenesis through the adenoma-to-cancer sequence was demonstrated. By integrating host transcriptomics, gut microbiome analysis, and metabolomics, it was demonstrated that the activation of UC metabolism in the host is accompanied by a lack of beneficial bacteria with urea hydrolysis, represented by Bifidobacterium bifidum, as well as an excess of pathogenic bacteria lacking urea hydrolysis. Mechanistically, urea can enter macrophages, inhibit phosphorylation signaling and the binding efficiency of transcriptional activator 1 (p-STAT1) to the promoter region of spermine/spermine N1-acetyltransferase 1 (SAT1), and further bias macrophages towards a pro-tumourigenic phenotype characterised by polyamine accumulation. Overall, UC, as an important pathway involved in host-microbiota metabolic interactions, shows potential diagnostic and therapeutic value in effectively overcoming CRC initiation [24]. In addition to this, the gut microbiota and its metabolites have been linked to cancer development and progression, as exemplified by targeted studies of therapeutic interventions in combination with cannabis treatments, where cannabis-based therapies in combination with strategies to modulate the gut microbiome (e.g., probiotics, prebiotics, or dietary interventions) are expected to enhance the anticancer properties of the cannabinoids [25].

4.2 Cancer inhibition

On the other hand, members of the gut microbiota can inhibit tumour development. They achieve their anti-tumour effects through the production of short-chain fatty acids, activation of the immune system, or modulation of the intestinal environment. It has been found that some probiotics can stimulate the activity of immune cells and improve their ability to recognise and attack tumour cells. The immunosuppressive tumour microenvironment (TME) exhibits significant heterogeneity and is a key promoter of tumour progression. Key components of the immunosuppressive TME, such as myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages, and regulatory T cells (Treg), attenuate the immune response during tumour progression, metastasis, and treatment resistance. MDSCs are composed of polymorphonuclear MDSCs (PMN-MDSCs) and monocyte MDSCs (M-MDSCs), which are known for their ability to suppress the immune response to tumour progression and metastasis by producing high levels of Arginase 1 (ARG1), Reactive Oxygen Species (ROS) and Nitric Oxide (NO) to inhibit T-cell proliferation and activation, which is involved in promoting tumour angiogenesis. Macrophages are divided into two different polarised states; M1-like macrophages have anti-tumour activity, whereas M2-like cells have pro-tumour and immunosuppressive properties. They express ARG1, which acts to process and deplete L-arginine, a process important for T-cell function. Tregs can induce an immunosuppressive phenotype and promote tumour progression [26]. The gut microbiota plays a crucial role in mediating the oncogenic effects of different compounds in the gut [27-29]. Controlled experiments were done in Wynder's group on germ-free and conventional rats to study the effect of gut flora on colonic susceptibility to the carcinogenic effects of 1,2-dimethylhydrazine. Only 20% of germ-free rats developed colon tumours, whereas 93% of conventional rats developed multiple colon tumours. Dysregulation of gut microbial ecology was observed in the intestines of both spontaneous and chemically induced colon tumourigenesis mice. For example, ApcMin/+ mice, a familial model of colon tumour disease, spontaneously develop intestinal tumours due to mutations in the adenomatous polyposis coli (APC) tumour suppressor gene [30]. Pientzehuang (PZH) inhibited colorectal tumour development in a dose-dependent manner in azoxymethane plus dextran sodium sulfate-treated mice and Apcmin/þ mice. The paper indicates that the chemopreventive effects of PZH involve both microbe-dependent and non-dependent mechanisms. Fecal microbiota transplantation from PZH-treated to germ-free mice partially recapitulated the chemopreventive effects of PZH. The PZH components ginsenoside- f2 and ginsenoside- re inhibited colorectal cancer cells and primary organoids, and PZH also inhibited tumourigenesis in azoxymethane-plus-dextran sulfate-sodium-treated germ-free mice [31].

4.3 Summary

The experiments of Cheng Y and Cou H demonstrated that the intestinal flora can indirectly inhibit tumour growth by suppressing gene mutations or being affected by other drugs, in addition to which there are many other unexplored mechanisms to inhibit tumour development that should be explored.

5. Conclusion

With the widespread use of immunotherapy in the treatment of tumours, the impact of the gut microbial community is of increasing interest. Certain gut bacteria enhance the efficacy of immunotherapy, while others may diminish its effect. For example, probiotic supplementation can enhance the efficacy of immunotherapy, whereas overgrowth of certain gut bacteria may be associated with immunotherapy resistance. Gut flora undoubtedly plays a pivotal role in the predictive value of immunotherapy efficacy, and an in-depth understanding of the relationship between gut flora and immunotherapy, and the translation of the relationship into clinical application and guidance is a current research priority. From the promotional and inhibitory relationship between intestinal flora and tumours to the mechanisms by which intestinal flora influences tumour development, the challenges that still exist are the influencing factors of flora and the exploration of comprehensive and in-depth mechanisms. The intestinal flora needs to be analysed based on existing bioinformatics technology, and the mechanism of bacterial strains in the intestinal tract affecting tumour development is also progressing slowly, which has become a speed-limiting bottleneck for this research. In conclusion, through the accumulation of sequence data of intestinal flora, we can establish an efficient and concise sequence database of intestinal flora, explore the correlation between intestinal flora and tumour, and apply the effect of intestinal flora on tumour to the intervention and treatment of chronic diseases, in order to complete the transformation of intestinal flora from scientific research to application.

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