Saudi Toxicology Journal (STJ)

Journal home page: https://uqu.edu.sa/s.toxicology.s/S.T.J

Review

Exploring the Mechanistic interplay between Chronic Inflammation and Gastrointestinal Cancer in the Gut Microbiome: A Review

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Citation: Abd Elmoneim, H. M. Exploring the Mechanistic interplay between Chronic Inflammation and Gastrointestinal Cancer in the Gut Microbiome: A Review. *STJ*, **2025**, 2, 14 – 31 https://doi.org/10.70957/uqu.edu.sa/s.toxicology.s/stj.2025.2.3

Received: 01 February 2025

Accepted: 06 March 2025

Published:

Abstract:

There are complex and heterogeneous immunological milieus of the gastrointestinal system, so there is a high mortality rate from malignancies affecting the gastrointestinal system. The pathophysiology of cancer has long been thought to be significantly influenced by inflammation. However, several of the mechanisms underlying its tumor-promoting activities have only lately been discovered. Both beneficial and harmful microorganisms play a crucial role in controlling the host immune system and, eventually, inflammation. Furthermore, bacteria may also influence how a tumor develops through different mechanisms, including long-term inflammation activation, changes to the tumor microenvironment, and genotoxic response induction. A significant percentage of cancers are caused by microbial species; according to conservative estimates, infectious pathogens are responsible for at least 15% of all cancer cases. The role of the gastrointestinal microbiota in the emergence of cancer is not well understood. This review will include a broad overview of commensal microbiota, inflammation, cancer, and the role of bacteria in these developing fields.

Keywords: Inflammation, Gastrointestinal cancer, Microbiota.

1. Introduction

One of the most common cancers to be diagnosed is gastrointestinal cancer. Cancer is a complex, genetic illness that is impacted by both environmental and host factors. The stomach, liver, pancreas, esophagus, anus, small intestine, large intestine (colon and rectum), and other portions of the Gastrointestinal tract (GIT) can all be affected by these cancers. Globally, GIT cancers are responsible for a significant portion of cancer cases and fatalities [1, 2].

It has been established that inflammation occurs in the tumor microenvironment, and that chronic inflammation raises the chance of developing cancer [3, 4]. According to estimates, persistent infections and the resulting inflammation are linked to between 10% and 20% of malignancies. Viruses, fungi, and both commensal and pathogenic bacteria actively contribute to the growth and upkeep of the modern definition of the microbiome as an organ that supports and enhances the host organism's healthy operation [5]. The bacteria

that live there as well as their structural components, like metabolites and nucleic acids, are included in the traditional description of the human microbiome. The intestines, and particularly the large intestine, are home to the great bulk of the estimated 3.8×10^{13} microorganisms. A major finding recently, that the microbiome of malignancy is very different from the microbiome of normal tissues [5, 6]. In addition to physical and chemical variables, microbiological factors are one of the risk factor groups that might lead to the development of cancer. These factors typically occur before the development of both acute and chronic inflammation, as well as cancer. These factors include, Helicobacter pylori (H. Pylori) propensity to cause gastric cancer (GC), the human papillomavirus's propensity to cause cervical cancer, or the hepatitis virus's to cause liver cancer (LC) [7].

Exposed organs to the environment and air, such as the upper digestive and urogenital systems, are colonized by microbes. However, the bacterial makeup of tissue in each system varies greatly amongst human being, and this alterability is impacted by a person's heredities, food, use of antibiotics and drugs, and other environmental variables. Additionally, through intricate regulation of inflammation and immunological tolerance, the immune system influences the types and locations of microbiota [8]. Chronic inflammation is now recognized as a key mechanism for carcinogenesis, leading to the most common examples of gastric cancers secondary to gastritis, colorectal cancer in inflammatory bowel disease, and liver cancer with hepatitis [9].

Important sources of tumor-associated inflammation include metabolic alterations, cell stress, and cell death, which are caused by cancer cells or by therapy. The tumor microenvironment's ongoing production of different cytokines, chemokines, and growth factors promotes the growth, evolution, and survival of cancer cells as well as tumor vascularization and immunological dysregulation, all of which lead to the invasion, metastasis, and resistance to treatment of tumors [10, 11]. Therefore, the use of anti-inflammatory drugs, either by themselves or in conjunction with cytotoxic drugs and targeted therapies, is a promising approach to treating malignancies that are driven by inflammation. This strategy works well in several animal models, but in order for anti-inflammatory therapy to be genuinely effective, many obstacles must be addressed due to the complexity and adaptability of human malignancies and associated ecology [12, 13].

The mechanisms underlying chronic inflammation-induced carcinogenesis in general will be covered in this review. The goal of this work was to compile the most recent data regarding the connection between inflammation, carcinogenesis, and microbiome. A review of the literature was done for this purpose, with an emphasis on recent developments in the study of the human microbiome, specifically on certain bacteria, viruses, and fungi, and how they affect inflammatory process and cancer development.

2. The link between chronic inflammation and cancer

Chronic infections are responsible for up to 10–20% of all malignancies. In terms of more general development, persistent inflammation at the cancer site precedes up to 20% of all malignancies. liver cancer and viral hepatitis [14], colorectal cancer (CRC) and inflammatory bowel disease (IBD) [4, 15], and GC and H. Pylori provoked inflammation are examples of this relation [16]. However, inflammation's function may be not restricted to its activity during tumor start and progression; it was triggered during growth of malignancy prompted inflammatory changes or in reaction to cell death and anti-cancer therapy [17]. Inflammation happens in reaction to direct trauma or external factors such as toxins or microbiomes. Tissue-resident immune cells cause acute inflammation by drawing neutrophilic granulocytes and macrophages when they become activated. T and B cells. Even solid tumors that appear to be non-inflammatory have the amazing capacity to attract immune cells and increase pro-inflammatory chemokines and growth factors, then additionally affects the development and tumor spread [3, 7, 18]. Acute inflammation reply, which includes phagocytic response and the release of chemokines that terminate and eliminate many threats. However, when the exogenous agent remains, chronic inflammation can occasionally occur, which can result in chronic disease. The idea of autoimmunity may have originated from the fact that the foreign factor in many chronic inflammatory disorders remains unknown. Nonetheless, there are reasons to question whether immune system malfunctions are the primary cause of many of our most significant illnesses. It seems more likely that the foreign substance triggering the immune

cells has not yet been discovered. But in a broader sense, chronic inflammation leads to the synthesis of growth factors that promote the growth of recently discovered tumors and make them act like non-healing wounds. Nonsteroidal anti-inflammatory drugs, anti-infective agents, and other widely used medications that can reduce inflammation, like metformin and statins, have been shown to lower the incidence and risk of cancer [19, 20].

Epigenetic changes that promote malignant progression and even start carcinogenesis can occasionally result from tumor-associated inflammation, which involves complex interactions between stromal and epithelial cells. [21]. For instance, reducing inflammation primarily inhibits the growth of tumors rather than destroying cancer cells; consequently, it must be used in conjunction with cytotoxic medications that are specific to cancer to completely eradicate the tumors. Additionally, anti-inflammatory medications can cause bystander effects on non-cancerous tissues due to the depletion of general survival factors. This can lead to tumor microenvironment remodeling, therapy resistance, and an increased vulnerability of non-malignant cells to non-specific cytotoxicity, which can result in toxicities [22, 23].

Effective therapies based on triggering anti-tumor immune responses have grown during the last ten years, such as immunological-checkpoint inhibitors or genetically modified T cells. A small percentage of patients experience long-lasting responses from these immunotherapies, while the great majority develop natural or acquired therapeutic resistance [12]. A pro-inflammatory and immunosuppressive tumor microenvironment (BOX1) is frequently responsible for immunotherapy resistance. Anti-inflammatory medications that target immunosuppressive cells or cytokines may increase the cancer's vulnerability to immune-mediated rejection in this situation. Furthermore, selectively treating the main causes of immunotherapy-induced inflammation may enhance the response-to-toxicity ratio and, consequently, therapeutic results, much like it does in the treatment of autoimmune illnesses [12, 24]. As a result, the combination of immunotherapy and anti-inflammatory medication may prove to be an effective strategy for overcoming the challenges posed by existing therapeutic approaches. Inflammation affects every step of cancer development and treatment, making it a classical cancer hallmark. Numerous reviews have addressed the key inflammatory mediators that control cancer-autonomous intracellular regulation and intercellular communication inside the tumor microenvironment [25, 26].

It has been acknowledged that the proinflammatory factors IL 1 and IL 6 from tumor-associated macrophages encourage the invasion of cancer cells, most likely due to the up-regulation of their receptors. For many types of cancer cells, IL-6 is thought to be an antiapoptotic agent [17]. Through the Jak-STAT3 signaling pathway, it also contributes significantly to the immunosuppressive process and tumor formation linked to chronic inflammation. In terms of structure or cellular function, IL 1, which comprises the two subtypes of IL 1α and IL 1β, has distinct characteristics. While IL 1β has been shown to harm inflammatory tissue and encourage tumor invasion, IL 1α is thought to produce anticancer immunity. It has been established that innate immune cells are negatively regulated by IL 10 and IL-6, which eliminate tumor cell immunity. Nonetheless, a few researchers have discovered that the tumor niche's high levels of IL 10 work to inhibit angiogenesis and encourage the death of cancerous cells [6, 10]. Additionally, TNF-α is highly expressed in tumor cells and has been linked to inflammatory-involved carcinogenesis. Tumor associated macrophages and other inflammatory cells can also create it, and it subsequently uses the nuclear factor kappa B (NF-κB) signaling pathway to help tumor cells survive. It has also been proposed that IL 17 has a significant role in the tumor environment, particularly in inflammatory-associated diseases. It is further demonstrated by promoting angiogenesis in tumor tissue, which in turn encourages the growth of further tumors [9, 20, 27]. **Figure 1**

3. A relationship between microbiota and cancer

An estimated three trillion bacteria reside in the human body, where they coordinate a wide range of physiological functions and disease vulnerabilities. Even though the number of bacterial cells in the body is comparable to that of human cells, greater genetic diversity of bacteria results in exceptional mechanistic and metabolic capabilities that affect host tissue-specific and immune cell functions in addition to their own microbial niche [28]. Under healthy conditions,

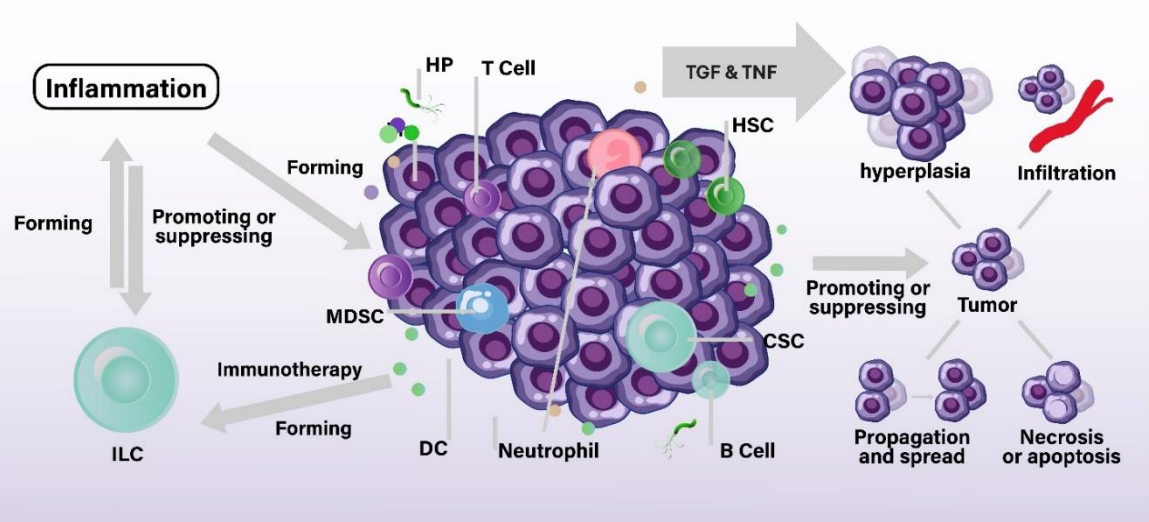

Fig.1 Inflammatory response to cancer and chronic inflammation: Shaping tumor immunity

Inflammation has a synergistic effect on the tumor immune microenvironment, promoting or inhibiting tumor proliferation, invasion, metastasis, and death. The progression of inflammation to malignancy is controlled by innate lymphocyte cells. In addition, inflammation alters the kinds and functions of innate lymphocytes. Because of their remarkable flexibility and distinct function in many phenotypes, targeting innate lymphocyte cells with immunotherapy is a viable technique for cancer prevention and control.

CSC: Cancer stem cell, DC: Dendritic cell, Hp: Helicobacter pylori, HSC: Hepatic stellate cell, ILC: Innate Lymphoid Cells, MDSC: Myeloid-derived suppressor cells, TGF-β: Transforming growth factor, TNF: Tumor Necrosis Factor

the host and its microbiome function as metaorganisms in symbiosis, offering a nutrient-rich milieu in exchange for assistance with digestion and metabolism [29]. Bacteria, viruses, fungus, and other microorganisms make up the individual microbiome, a multifarious flora and fauna of microorganisms that live inside the body [30, 31]. Microbiome groundbreaking research has clarified the microbiome's vast diversity and functionality, highlighting its importance in promoting health and influencing the etiology of disease [32, 33]. The microbiome, which is especially abundant in the gastrointestinal system, is essential for many physiological functions, such as digestion, immunological response, and even brain and behavior [34, 35]. Beyond infectious diseases, it affects a wide range of human illnesses, including malignancies, metabolic disorders, neurological diseases, allergies, and cardiovascular issues. With data indicating that dysbiosis, an inequity in infective groups, can impact the development of autoimmune diseases and the response to contagious diseases, further study has expanded knowledge of the microbiome's function in immunity [23, 36, 37]. Furthermore, the complicated correlation between microbes and cancer has been shown by recent developments in sequencing technology and microbiome research, generating a great deal of concern in their possible responsibilities in developing and progression of malignancy [22, 38-40]. Recent data suggests that bacteria, which are found in the tumor microenvironment, influence carcinogenic processes in a variety of ways, such as by producing carcinogens, modifying host inflammation, and changing the tumor microenvironment. Throughout the digestive system, a constantly changing and intricate bacterial environment highlights the importance of bacteria in digestive system tumors [11, 41, 42].

Depending on how they interact with host cells and the surrounding environment, these bacteria can both promote oncogenesis and act as protective agents against carcinogenesis in digestive system tumors [43, 44]. One example of the substantial influence of

bacteria on the formation of GIT malignancies is the correlation linking H. pylori infectivity and carcinoma of the stomach [16]. On the other hand, by generating fatty acids from dietetic fibers, specific bacterial communities within CRC may advantageously influence immune reactions, indicating the prospective of nutritional treatments in CRC care [45, 46]. Crucially, microorganisms have a substantial impact on patients' responses to treatment and prognosis, going beyond the onset and progression of cancer [13].

By altering the tumor microenvironment, affecting medication, and intermingling with the presenter immunity, intratumoral bacteria can improve or reduce the effectiveness of current treatments. Some bacteria seen in CRC have been linked to increased effectiveness of immune therapy, possibly because of their influence on the immunological factors, which favors T cell infiltration and activation [47]. This finding emphasizes how microbiome analysis may be used to inform treatment choices and forecast immunotherapy response. Furthermore, it has been discovered that some bacteria metabolize chemotherapy medications, such gemcitabine, which lowers the medication's availability and effectiveness in treating pancreatic cancer [48]. For instance, better prognosis has been linked to a lower variety of bacteria in CRC, potentially because of the positive effects of microbial miscellany on immunity modulation [27, 49]. All together, these results emphasize the significant effects of bacteria in malignancies of the colon and rectum, with implications for incorporating microbiome investigate into the management of cancers of the digestive system [50, 51].

4. Microbiota and cancer progression: inflammation as a driver

The disturbance of the epithelial barriers of tissues, which permits bacteria to flow into partitions that are not typically nearby microorganisms, is a commonality among illnesses wherein microbiota contributes to deterioration. Due to permanently damaged tissue and an ongoing flow of microbial products and microorganisms, this might cause a localized chronic inflammatory response. The underlying mucosal barrier is broken in IBD and CRC, for instance, a rapid growth of tumor cells exposes the colon and inhabitant immune cells to a high concentration of antigens and toxins that are produced by microorganisms [22, 41]. Pro-tumorigenic cytokines, which can function as growth factors, trigger abrasion restorative processes, cause invasion, and encourage angiogenesis, thus quickening the formation of tumors. According to a recent study, in colon adenoma animal models, commensal microbiota causes IL 6, IL 23 and IL 17 signals because of abnormalities in the integrity of the colon barrier. Antibiotic therapy or genetic abrogation of IL 23 stops carcinogenesis [22, 52]. Similarly, it was demonstrated that intestinal barrier abnormalities in mice transgenic animals, which are prone to polyp development enable microorganisms to cause neutrophil buildup and inflammation, which encouraged the development of cancer. The significance of microbiota in neoplastic transformation is demonstrated by the possibility that polyp formation could be reversed by antibiotic therapy and re-induced by reintroducing stool from mice that had polyps [6, 53].

In CRC models, regulation of IL 22 signals has been shown to be significant. In colon damage, IL 18 was demonstrated to down-regulate IL 22BP, allowing for a surge in IL 22 signals that, if unbridled, encouraged tumor development. In a microbially driven CRC model, it was also demonstrated that blocking IL 22 signals decreased tumor burden and inflammation. Commensal antibiotic depletion reverses the effects of matriptase depletion by restoring colon shape, increasing mucin synthesis, and decreasing infiltrating inflammatory cells. In colitis-associated cancer mouse models, commensal E. coli upregulates IL 17C production, which promotes tumor cell development by inhibiting apoptosis, inducing BCLXL, and attracting tumor-promoting lymphocytes [45, 54]. By ablation of inflammasome proteins and bacterially driven up-regulation of CCL 5 from epithelial cells, it selects microorganisms for colon that cause progressive colitis and colon inflammation associated with cancer progress. This leads to an influx of immune cells that produce IL 6 and increased epithelial proliferation. In addition to blocking the impact of transplanted colitogenic microorganisms, the inhibition of IL 6 signals dramatically lowers inflammation and tumor load. These outcomes impart credence to the idea that bacterial localization plays a crucial role in controlling colon inflammation and that a microbiota can encourage cancer growth is the disruption of epithelial reliability [36, 55]. These investigations and therapy in cancer animal research, and blockage of the organism

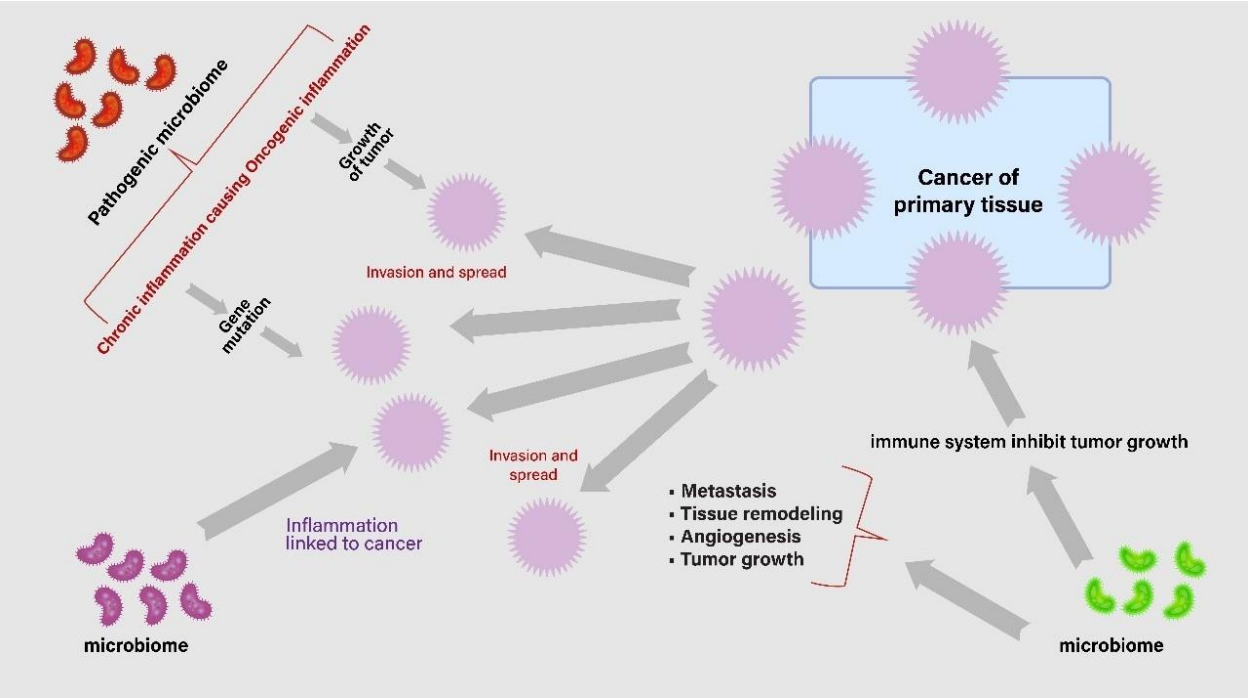

Fig. 2 Inflammation and microbiomes contribute to tumor development, progression, and metastasis

By increasing genetic instability and fostering a milieu that supports tumor growth, the microbiome both directly and indirectly affects the body's inflammatory response and maintenance, which in turn promotes the growth of malignancies. Along with influencing the immune response mechanisms that control tumor start and progression, the microbiome may also have an impact on the development of cancer-promoting factors including obesity and metabolic syndrome.

perception paths (TLR/MyD88) all clearly show that commensals can worsen the progression of CRC. The role of commensal bacteria and immunological tolerance in the colon has been the subject of numerous recent investigations. $APC^{\Delta 468}$ animals treated with dextran sodium sulfate are protected against intestinal polyp development caused by microbes by T-cell-derived IL 10. Mice with T-cell-specific IL 10 ablation have fewer pro-tumorigenic eosinophilic infiltration and adenomatous polypi. Commensals have also been demonstrated to support wound restoration, which is marked by initial inflammation followed by epithelial control, thereby preventing inflammation and, consequently, inflammation-associated carcinogenesis [5, 37, 56, 57]. In germ-free mice, epithelial proliferation is delayed followed by hyperproliferation, and the epithelium never seems to heal. Remarkably, in these germ-free mice, TLR/MyD88 deletion reduces colon inflammation and slows tumor progress, indicating that the TLR/MyD88 system may have both independent and microbe-dependent processes as warning signals. Therefore, it is possible to induce tumor-promoting inflammation without the presence of microbes and yet indorse inflammation linked to cancer. This suggests that the necessity of inflammation for tumor growth outweighs the possibility of microbes directly promoting tumor growth, meaning that in many cases, microbes are required to induce inflammation rather than directly acting on cancerous cells. Therefore, the promotion or suppression of cancer depends critically on the steadiness among inflammation, the host immunity, and microorganisms [47, 58, 59]. **Figure 2**

5. Esophageal cancer (EC)

Recent studies on esophageal microbiome have shown notable changes in EC patients, which may indicate that the microbiome plays a role in the development of this cancer. The microbial makeup of healthy people, Barrett's esophageal (BE) patients, and EC have been clearly distinguished from one another, underscoring the dynamic changes that occur as the disease progresses [60]. The observed decline in microbial diversity in EC patients, which is typified in change from the occurrence of Veillonella and Streptococcus

to the preponderance of Lactobacillus, is very significant [61-63].

It is thought that this change has a major effect on the tumor microenvironment and may aid in the development of tumors. Using DNA sequencing, additional examination of the microbial diversity in EC tissues revealed a marked decline in comparison to nontumor tissues, along with a rise in Fusobacterium abundance and a comparable drop in streptococcus [64]. With early detection and progression monitoring, Streptococcus and Neisseria together have been found to be highly predictive of EC progression and its precancerous lesions through innovative research employing microbial prediction models [65]. The amount of Fusobacterium nucleatum DNA in EC tissues is noticeably higher than in normal esophageal mucosa, according to later research encompassing 325 resected EC specimens. Its capacity as a predictive biomarker in EC was demonstrated by the high correlation found between Fusobacterium nucleatum DNA and late tumor stages, and a shorter survival rate for cancer-specific patients, has been documented. Furthermore, a strong association between Fusobacterium nucleatum and the chemokine CCL20 has been noted, pointing to a possible mechanism by which the bacteria could encourage tumor aggressiveness [66]. Additionally, Porphyromonas gingivalis has been found to be more common in EC tissues, however its prevalence varies according to the stage of EC. Its prognostic significance is further highlighted by the fact that its presence is frequently linked to poor tumor differentiation, advanced stages, metastasis, and decreased survival outcomes [67, 68]. With various microbial compositions associated with variable responses to chemotherapy and radiation therapy, there is growing evidence that the esophageal microbiome plays a role in regulating responses to immune checkpoint inhibitors in EC [69]. These findings emphasize the complex interaction among bacteria and the host immunity in EC and the ability for microbiome affected therapeutics to enhance patient outcomes and therapeutic efficacy in addition to conventional cancer treatments [70, 71].

6. Gastric cancer (GC)

6.1. Inflammatory Gastritis and Helicobacter Pylori as Carcinogens

H. pylori infestation being the supreme obvious risk factor, linked to almost GC patients, and initiating pathologic pathways essential to the tumor's course, GC poses a serious threat to global health [72, 73]. These techniques include causing DNA damage, disrupting autophagy pathways, triggering a persistent inflammatory response, and influencing the host's innate immune system [74-76]. More than half of people worldwide have H. pylori colonizing their stomach mucosa, but only a small percentage get GC, indicating a complicated interaction between the bacteria, the host, and the environment. In the stomach mucosa, for instance, an H. pylori infestation triggers a chronic inflammation that is typified by the enrollment of inflammatory cells and the release of cytokines including TNF-α, IL 1β, and IL 8. Inflammation creates a favorable setting for tumor development, which is thought to be a prelude to atrophic gastritis, a known risk factor for GC [77-79]. Furthermore, H. pylori secrete virulence factors that control host cell proliferation and death, most remarkably vacuolated cytotoxin A (VacA) and cytotoxin-associated gene A (CagA) [80, 81]. Following inoculation in host cells, CagA is phosphorylated and intermingles with transduction paths, resulting in increased mutations, proliferation, and dysregulated cell signaling. The generation of reactive oxygen and nitrogen species generated that cause oxidative stress and genomic instability in important genes implicated in gastric carcinogenesis, H. pylori infestation is also linked to augmented DNA impairment in gastric epithelium [82-85].

Research also examines how H. pylori affect gastric microbiota, indicating that dysbiosis brought on by H. pylori may possibly be a factor in the development of cancer. Reduced stomach microbial miscellany is consistently seen in intestinal metaplasia, atrophic gastritis, and GC, indicating a dysbiotic shift that favors carcinogenic processes [86, 87]. On the other hand, some research indicates that individuals with GC have higher levels of microbial evenness and diversity than patients with other types of gastritis, suggesting a complicated link between microbial diversity and the development of cancer [88]. Microbial miscellany and magnificence inside tumor micro territory s have significantly decreased, according to recent studies that focus on microbial sketching from normal gastric epithelium to carcinoma in humans [89, 90].

Additionally, several disordered bacterial bunches can discriminate between gastric inflammation and carcinoma, emphasizing their prospective for prompt

recognition. Furthermore, there is prognostic importance to the differences in gastric microbiota across GC patients; for example, several bacteria, such as Prevotella and Fusobacterium, are strongly linked to lower overall survival rates, indicating that they may be prognostic targets [90]. The necessity for a thorough identification of cancer promotion that considers not only harmful H. pylori on the contrary larger organism ecology is highlighted by research on the involvement of the stomach microbiome in GC. By specifically modifying the stomach microbiota, this method has the potential to transform GC management and offer new opportunities for diagnostic, prognostic, and therapeutic approaches [91, 92].

7. Colorectal cancer (CRC)

The gut microbiota plays a critical role in the carcinogenesis of CRC, as evidenced by the growing number of extensive metagenomic investigations in this disease that have highlighted species-specific changes in microbial composition and ecology [93]. The gut microbiome plays a role in the development and advancement of CRC through a variety of intricate processes, as evidenced by the high correlation between gut microbial dysbiosis and CRC pathogenesis. For example, Fusobacteria, which are frequently present in the human mouth [94, 95], have been discovered to be more prevalent in CRC tissues than in healthy controls, which may indicate that they play a part in encouraging the creation of tumors and the advancement of CRC [96, 97].

Pathogenic microorganisms can provide reliable biomarkers to learn more about pathologic illness, how it is treated, and how to manage it. Recent research indicates that noncoding RNAs (ncRNA) regulate a number of processes related to cell division, proliferation, and apoptosis, including the composition of the gut microbiota, and hence have a significant role in the development of cancer. ncRNAs are interesting avenues for future research in areas like medicines and diagnostics. ncRNAs' involvement in GIT cancer. Several Escherichia coli (E coli) bacteria have been demonstrated to favorably contribute to colorectal cancer development in a manner that depends on microRNA (miRNA). While pathobionts may raise the expression of oncogenes, probiotics may decrease the expression of oncogenes and increase the expression of tumor suppressors [98]. These miRNAs are essential for the development of colorectal cancer and microbiota-mediated colorectal carcinogenesis. The microbiome is influenced by diet and eating habits, and this plays a significant role in initiating the link between nutrition and cancer. However, tumor-associated miRNAs can control both the alteration in metabolism and the development and makeup of the gut microbiota. The microbiome's metabolites, including miRNAs, could alter gene expression. Gut microbiota-miRNA crosstalk is essential for maintaining gut homeostasis. Dietary or intestinal epithelial cell-secreted miRNAs can affect the composition of the microbiota. The composition of the microbiota and the released miRNAs are regulated in both directions. Because miRNAs and bacteria may interact therapeutically, miRNA delivery may be investigated as a therapeutic approach [99, 100]. **Figure 3**

According to recent studies, CRC is characterized by an overexpression of the host factor D-galactose-β-N-acetyl-D-galactosamine, which facilitates Fusobacterium enrichment in CRC via attaching itself to the surface of Fusobacterium nucleatum and interacting with the galactose-binding lectin Fap2. This relationship encourages CRC metastasis, highlighting how important host-microbe interactions are to the development of CRC [101]. Furthermore, Fusobacterium nucleatum promotes invasion, inflammatory reactions, and CRC cell proliferation by fastening its FadA adheres to E-cadherin on malignant cells, activating β-catenin signaling and aiding in the oncogenesis of CRC. By activating the TLR4/MYD88 cascade in cells, Fusobacterium nucleatum mechanistically activates NF-κB pathway, which in turn causes the expression of downstream target microRNA 21 to be upregulated [95].

Fusobacterium nucleatum then controls the downregulation of RAS p21 protein activator 1 mediated by microRNA 21 to increase the spread and multiplying of CRC cells by activating the MAPK pathway. Crucially, advanced CRC characteristics such as late stage, increased Ki-67 expression, and lymphatic spread are linked to greater levels of Fusobacterium nucleatum and microRNA 21, which lowers overall survival rates in CRC patients [27, 102]. These results have significance for prognosis prediction and therapeutic care as they point to a strong correlation between Fusobacterium nucleatum richness and worse scientific consequences in CRC.

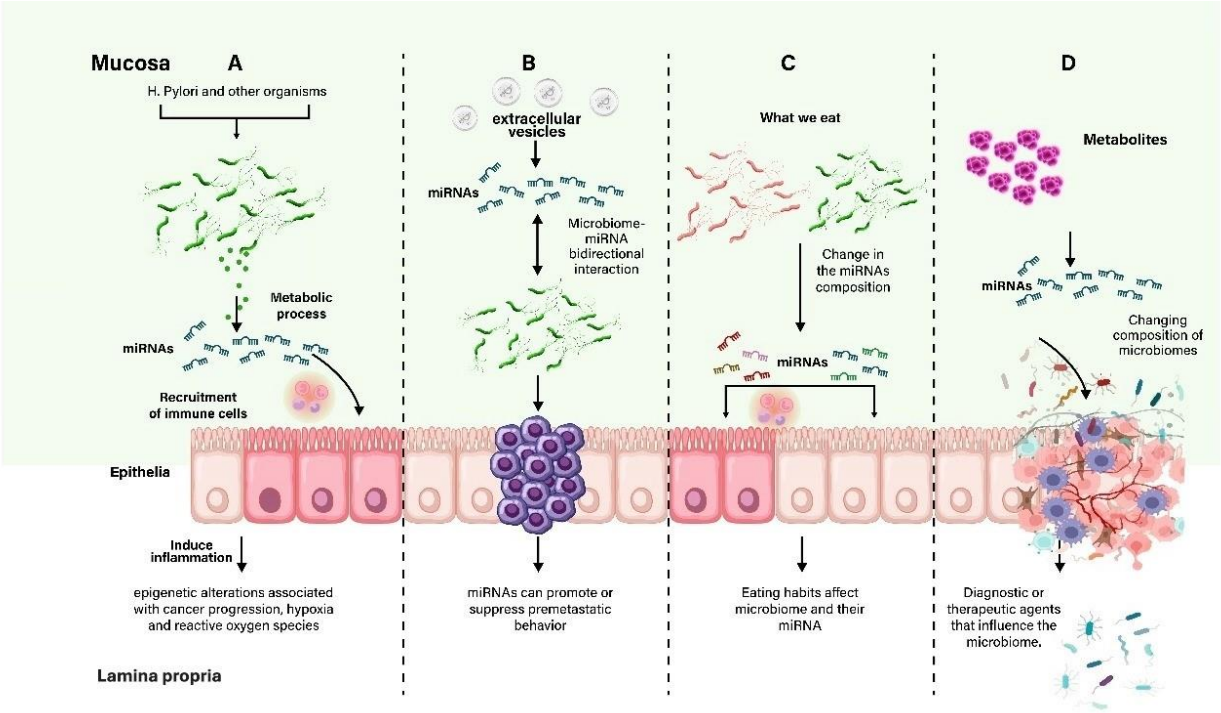

Fig. 3 Tumor suppression and oncogenesis: a model of the gut microbiome and microRNAs

(a) The composition of the microbiome can affect microRNA expression and cause immunological recruitment, inflammation, and epigenetic changes linked to the advancement of cancer; (b) In order for cancer to develop, microRNAs and the microbiota must interact in a bidirectional manner; (c) The diet habits you adopt can have a profound impact on the composition and expression of your microbiome; (d) There are a number of ways to use non-coding RNA as therapeutic agents that influence the composition of the microbiome or as diagnostic tools.

Additionally, Fusobacterium nucleatum creates evasion strategies by preventing natural killer (NK) cells from infiltrating and causing cytotoxicity in CRC tumors. The repressive receptor T cell immunoglobulin and ITIM domain on NK cells interacts with the Fap2 protein of Fusobacterium nucleatum to limit NK cell function, thereby shielding human colon tumors from immune cell assault. Similarly, research has shown that Bacteroides fragilis plays a causal role in CRC [103, 104]. The development of CRC is facilitated by enteropathogenic E coli infection, which causes the effector protein EspF, which is secreted by E coli, to migrate to the host cell membrane and mitochondria. This depletes DNA mismatch repair gene and increases frequency of impulsive mutations [105]. Furthermore, through STAT3/NF-κB/IL 17R signaling, Enterotoxigenic Bacteroides fragilis (ETBF) releases Bacteroides fragilis toxin (BFT) to trigger colon epithelium. This results in the recruitment of CXCR2-expressing polymorphonuclear immature myeloid cells and Th17 cell response, which in turn triggers inflammation that promote colon cancer and myeloid cells that are necessary for this development. These results show that bacteria can alter the immunological milieu of the tumor, which promotes the development of CRC [15, 106].

Whereas the malignancies associated with IBD begin as flat dysplasia, the most common kind of colorectal cancer advances through adenomas or polyps. Additionally, these two forms of colonic cancer have different genetic alterations [107]. Ulcerative colitis (UC) leaves individuals at risk for colon cancer after chronic illness. This connection has been known for many years and is among the best proofs that inflammation plays a significant part in the development of cancer. Since the cause of ulcerative colitis is likewise unknown, it is not surprising that the mechanism underlying this carcinogenesis is unknown. However, UC patients with complete colitis, in which most of the colon is damaged, have a higher risk of cancer, although patients can ignore this risk rise associated rectum-specific inflammation. Individuals who have UC and primary sclerosing cholangitis (PSC)

are especially vulnerable to colonic cancer that is restricted to the proximal colon, which may only exhibit subclinical inflammation [108, 109]. PSC prejudices patients to cholangiocarcinoma and UC predisposes patients to colonic cancer suggests that inflammation, rather than local factors, is the carcinogenic cause. There is consensus that prolonged active inflammation raises the risk, even though patients may develop colon cancer after decades of inactive UC. For example, a virus may be the cause of UC which might be a factor in the development of cancer [110-112]. It's interesting to note that the etiology of IBD has also been considered in relation to bacteriophages [113]. Furthermore, when inflammation affects the colorectal organ, people with Crohn's disease (CD) are more likely to develop CRC, while their risk is smaller than that of patients with UC [114]. However, the cause of the inflammatory response may be linked to the nerves, most likely ganglion infection, as CD may have a segmented dispersal with engrossment of the mesentery [115].

Because it might take more than 8 to 10 years from the onset of colitis to the diagnosis of cancer, the onset of IBD in the elderly does not necessarily indicate an increased risk of colonic cancer [116]. Although the relatively new tactic of causing deep or histological remission is intriguing, it is impossible to assess how it affects carcinogenesis over several years. Lastly, with regard to the etiology, it is hoped that in the future, the connection between IBD and pyoderma gangrenosum [117] and alopecia areata [118] will be clarified. A more recent definition of microscopic colitis is a condition marked by persistent inflammation. The risk of colon cancer has drawn attention. In several epidemiological studies, the risk of colon cancer appears to be lower or comparable to the background population despite chronic inflammation [119]. Therefore, the origin of inflammation, which is regrettably unknown currently, determines the elevated risk of colon cancer in patients with chronic, long-term inflammation [120].

8. Liver cancer (LC)

It is becoming more and more clear that gut microbiota and the onset of LC have a complex relationship that is regulated by both systemic and local variables. The liver is an important location receiving nutrients from the intestinal wall interact with the gut microbiome and microbe-associated molecular patterns. Usually, microbial metabolites and by products make up these associated molecular patterns [121]. Numerous studies have demonstrated the crucial roles that intestinal absorbency and dysbiosis play in promoting the development of hepatic disorders that lead to liver cancer, emphasizing the reciprocal control and interdependence of these variables [58, 122].

. Notably, an increase in fecal microbial diversity indicates the development from chronic hepatitis by B virus (HBV) induced liver cirrhosis to carcinoma. This includes a decline in butyrate-producing genera and an increase in the Phylum Actinobacteria and lipopolysaccharide constructing species. About 80% are beneath the curve for early detection of cancer model that used microbiota with different appearance and was confirmed in 486 fecal analysis from various locales, suggesting the capacity of microbial outlines in primary cancer diagnosis [123, 124]. Furthermore, patients with HBV-related hepatocellular carcinoma (HCC) have considerably higher fecal microbial richness than both controls and patients with non-hepatitis C virus associated with HCC. E coli and Shigella are more abundant in fecal samples from patients with virus infection related to HCC, but Bacteroides, Ruminococcus, and Lachnoclostridium are less prevalent [125]. Patients with carcinoma had higher ranks of Bacteroides and Ruminococcaceae and lower ranks of Akkermansia when compared to those with nonalcoholic steatohepatitis prompted liver cirrhosis without carcinoma [126]. Furthermore, it has been confirmed that intestinal leakage occurs at different stages of the progression of chronic liver disease to HCC by the detection of elevated levels of lipopolysaccharides (LPS), a constituent of bacteria's cell walls, in blood samples, mouse models, and HCC cell lines [127]. In a high-fat diet-promoted non-alcoholic steatohepatitis mice model, increased intestinal permeability brought on by substances such as dextran sodium sulfate raises portal LPS levels and encourages tumor growth [128]. Additionally, increased intestinal bacterial translocation promotes the development of liver cancer by interacting with arrangement appreciation on host liver cells, to cause chronic liver inflammation [129]. Elevated LPS levels have a strong mitogenic effect on hepatocytes by stimulating the upregulation of epiregulin mRNA and protein in both human and animal hepatic stellate cells in NF-κB-dependent manner [130]. Furthermore, hepatocyte death is prevented by activating the LPS-

TLR4 axis, which reduces NF-κB-mediated cleavage of the apoptotic marker caspase-3 [106, 130]. Moreover, long-term activation of the LPS-TLR4 axis increases inflammation-mediated hepatocyte proliferation and tumorigenic response by promoting NF-κB activation and decreasing toxicity induced by reactive oxygen species[129].

In HCC cells, TLR4 expression produced by LPS directly triggers NF-κB signaling, which in turn promotes Snail and other key transcription factors convoluted in epithelial-mesenchymal transition (EMT) [49, 131]. As a result, EMT processes and spread in HCC cells are improved by snail induction. Notably, TLR4 is detected in specimens from 106 HCC patients, and a higher expression level is associated with a poorer prognosis, including a lower chance of surviving cancer-free or overall. Poor clinicopathologic features are strongly linked to TLR4 overexpression. Additionally, through bacterial metabolites, dysbiosis has been linked to the development of liver cancer. Additionally, through bacterial metabolites, dysbiosis has been linked to the development of liver cancer. Research using obesity-associated HCC mice models has shown that changes in the gut microbiota and elevated deoxycholic acid levels encourage the development of senescence-associated secretory phenotype in hepatic stellate cells. Inflammatory and tumor-enhancing substances such IL 6, CXCL1, and CXCL9 are released by this phenotype. Curiously, treatment with vancomycin, which aims gram positive bacteria, reduced senescence symptoms and braked the growth of carcinoma [131]. This suggests a rise in obese patient associated with gram positive bacteria may promote the progress of carcinoma by allowing gut bacterial compounds to circulate entero-hepatically. Crucially, patients with HCC who have nonalcoholic steatohepatitis have also shown signs of cellular senescence. Furthermore, liver antitumor immunosurveillance has been linked to gut bacteria-regulated bile acid metabolism. Gram-positive bacteria's function in bile acid transformation lowers the concentration of chenodeoxycholic acid and raises glycolithocholate which in turn lowers the expression of CXCL16 on liver sinusoidal endothelial cells. This imbalance promotes the formation of liver tumors by suppressing the accumulation of CXCR6 and NK cells and antitumor activity [132]. Similar bile acid regulation effects on CXCL16 expression have been verified in liver endothelial cells. Furthermore, during the development of icteric HCC, dietary soluble fibers and the short-chain fatty acids that are produced during fermentation show complex effects [133].

Mice models with Toll-like receptor 5 deficiency (T5KO), which are at risk for icteric HCC, exhibit gut dysbiosis marked by a surge in Proteobacteria and fiber-fermenting bacteria. In T5KO mice models, a high-fat diet enhanced with inulin causes gut dysbiosis, cholestasis to develop early, hepatocyte loss, neutrophilic inflammation, and ultimately icteric HCC. The incidence of HCC has been considerably decreased by targeted therapies meant to decrease bacterial fermentation, reduce solvable fiber consumption, or stop bile acid reabsorption. These results highlight the importance of aiming gut-microbiota in liver carcinoma therapy plans [134]. Preclinical research has demonstrated promise in reducing the development of HCC by focusing on the gut-microbiota-liver axis and implementing treatments that target LPS and its receptor TLR4 [135]. In HCC animal models, constant gut distillation with antibiotics such ampicillin, neomycin, metronidazole, and vancomycin successfully lower tumor size and quantity. Additionally, how the gut microbiota is altered affects how well immunomodulatory and chemotherapeutic treatments work [121, 136]. Several experimental animal models have shown the therapeutic potential of interventions such as fecal microbiota transplantation, TLR antagonists, and the usage of bile acids and receptors to preserve barrier of the intestine [137]. Although preclinical findings from mice and rats have been translated into clinical trials, there is still a gap between the promise of gut-microbiota-liver axis treatment options for HCC [136].

Both hepatitis B virus (HBV) and hepatitis C virus (HCV)-induced chronic viral hepatitis put patients at risk for liver cirrhosis and HCC. In addition to the inflammation itself, which is most likely the only mechanism for the carcinogenesis produced by HCV, HBV, being a DNA virus, integrates into the host genome and consequently contributes to hepatocellular carcinogenesis. Compared to children infected later in life, fewer children with prenatal HBV infection have cirrhosis and HCC [138, 139].

9. Therapeutics Targets

A deeper comprehension of the molecular mechanisms underlying cancer development will make it possible to incorporate therapeutic factors like probiotics and

prebiotics, use antibiotics more effectively, and manipulate bacterial proteins to permit or restrict particular features that cause the injuriousness and oncogenesis of particular bacterial species [140]. The exposome theory and its effects on the human body are important factors to consider when examining how the microbiome affects carcinogenesis. The exposome is made up of numerous interrelated components. An integrated function of the human body's exposure, the exposome encompasses everything that surrounds us, including our environment, our relationships, what we eat, the medications used, and hobbies we engage in. It is important to remember that exposure encompasses both chemical compounds made by the body during metabolic processes as well as substances or stimulants that we eat [141]. Consequently, the microbiome and its effects are significant exposome components that, to some degree, might lessen the adverse effects of specific exposome components on the human body. Prebiotics, which are indigestible food elements that specifically promote the growth of specific human-beneficial commensal bacterial strains. probiotics, which are live microorganisms that improve the intestinal microbiota's ability to operate. Both have become essential components of the daily diet and are used to prevent and treat several illnesses, primarily those affecting the gastrointestinal system. There have been findings demonstrating the favorable effects of dietary fiber on gut bacterial strains' production as well as its potential anti-cancer effects [27, 95, 119].

Studies on animals have demonstrated the capacity to suppress bacterial proteins without upsetting the host's microbial equilibrium. The disease's symptoms can be lessened by depleting bacteria containing certain proteins, including colibactin. Additionally, the impact of bacterial enzyme manipulation on human health was investigated. Patients who use the anticancer medication irinotecan experience persistent diarrhea, which reduces the likelihood of successful treatment. Inhibitors for the bacterial enzyme β-glucuronidase, which reactivates the conjugated forms of irinotecan and also causes diarrhea in patients, were created by Wallace et al. [142, 143]. As shown in a mouse model, β-glucuronidase inhibition decreased the harmful effects of chemotherapy without influencing commensal bacteria. The development of such inhibitors to combat the commensal bacteria's possible carcinogenic qualities without upsetting the delicate balance of the microbiome appears to be the next step in the future [92, 144].

10. Conclusions

An increased risk of cancer is linked to chronic inflammation in many gastrointestinal tract organs. It appears that inflammation occurs in tandem with or as a byproduct of more significant processes in the stomach, colon, and liver. A large portion of the genesis of malignant tumors of the digestive system can be prevented and controlled by reducing chronic inflammation. In-depth examinations of the GIT microbiome have linked microbial patterns to illnesses including cancer. To cure or prevent disease, microbes that have been modified to express genes or create metabolites may be introduced into specific GIT niches. An intriguing new area for the management and prevention of GIT cancers is microbiome. Targeting these opportunistic and dangerous microorganisms requires the development of novel medicines. Furthermore, by altering immune system reactions or preserving the reliability of the epithelial defense. In the future, therapeutic generation might be planned to counteract microorganisms causing malignancy as a start. The composition of the microbiome may influence the drugs, doses, or regimens prescribed to patients, or it might be used to monitor the effects of therapy on the microbiota. Even though there is still a lot to learn, this sector has witnessed some fascinating advancements recently, and we should anticipate major advancements soon.

Abreviations

Barrett's esophageal	BE
Colorectal cancer	CRC
Crohn's disease	CD
Cytotoxin-associated gene a	CagA
Epithelial-mesenchymal transition	EMT
Escherichia coli	E coli
Esophageal cancer	EC
Gastric cancer	GC
Gastrointestinal tract	GIT
Helicobacter pylori	H. Pylori
Hepatitis B virus	HBV

Hepatitis C virus	HCV
hepatocellular carcinoma	HCC
Inflammatory bowel disease	IBD
lipopolysaccharides	LPS
liver cancer	LC
MicroRNA	MiRNA
Natural killer	NK
Noncoding RNAs	ncRNA
Nuclear factor kappa B	NF-κb
Primary sclerosing cholangitis	PSC
Ulcerative colitis	UC
Vacuolated cytotoxin A	VacA

Funding: "This research received no external funding".

Informed Consent Statement: "Not applicable".

Declaration of Generative AI and AI-assisted technologies in the writing process:

During the preparation of this work the authors used ChatGPT 4.0 and Google Gemini in order to enhance the writing of this manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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