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Influence of the gut microbiota on immune cell interactions and cancer treatment

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Abstract

The tumour microenvironment represents a novel frontier in oncological research. Over the past decade, accumulating evidence has underscored the importance of the tumour microenvironment (TME), including tumour cells, stromal cells, immune cells, and various secreted factors, which collectively influence tumour growth, invasion, and responses to therapeutic agents. Immune cells within the TME are now widely acknowledged to play pivotal roles in tumour development and treatment. While some perspectives have posited that immune cells within the TME facilitate tumour progression and confer resistance to therapeutic interventions, contrasting conclusions also exist. Affirmative and negative conclusions appear to be context dependent, and a unified consensus has yet to be reached. The burgeoning body of research on the relationship between the gut microbiota and tumours in recent years has led to a growing understanding. Most studies have indicated that specific components of the gut microbiota, such as unique bacterial communities or specific secretory factors, play diverse roles in regulating immune cells within the TME, thereby influencing the prognosis and outcomes of cancer treatments. A detailed understanding of these factors could provide novel insights into the TME and cancer therapy. In this study, we aimed to synthesise information on the interactions between the gut microbiota and immune cells within the TME, providing an in-depth exploration of the potential guiding implications for future cancer therapies.

Keywords Gut microbiota, Tumour microenvironment, T cells, Macrophages, Immune therapy

Introduction

The tumour microenvironment (TME) is composed primarily of tumour cells, stromal cells, immune cells, endothelial cells, and various secreted factors. Its importance lies in the intricate network formed through communication and interactions between diverse cell types and secreted factors surrounding tumour cells. The heterogeneity of cell types and secreted factors within the TME enables modulation of the efficacy of anticancer drugs, thereby influencing treatment outcomes [1]. Notably, the immune cell population in the TME is crucial. These immune cells have been demonstrated to interact with tumour cells, promote tumour growth and metastasis, and confer immune escape properties [2, 3]. Immunotherapeutic strategies targeting immune cells within the TME are emerging as new possibilities for cancer

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treatment, leading to the development of a variety of therapeutic approaches [4].

The gut microbiota refers to the microbial communities that parasitise the human intestinal tract, and the compositions of these communities are determined by various factors, such as genetics, disease prevalence, and exposure to antibiotics. Alterations in the compositions of these microbial communities not only contribute to the onset of disease but also elicit systemic and local metabolic and immune responses. As research into this subject has become more sophisticated, the relationship between the gut microbiota and tumours has become increasingly evident, conferring implications for the occurrence, progression, and therapeutic responses of tumours [5]. One study showed that alterations in the gut microbiotic community and its associated metabolites could induce hepatocellular carcinoma in mice [6]. The application of modulations to the gut microbiota in cancer therapy has become a burgeoning area of investigation.

Recent research has indicated that existing cancer immunotherapies targeting immune cells do not uniformly improve patient prognosis and that there is considerable variability in treatment responses among individuals [7]. These findings underscore the importance of addressing how to increase the effectiveness of immunotherapies that target immune cells. Considering the impact of the gut microbiota on the TME, particularly on immune cells, it is plausible to explore whether manipulating the gut microbiota or targeting specific microbial alterations could improve the efficacy of immunotherapy. In this study, we aimed to compile and analyse the interactions between the gut microbiota and tumour-associated immune cells, as well as integrating immunotherapeutic approaches, with the intention of providing insights for future enhancements in immunotherapy.

The gut microbiota impacts tumour progression via its associated metabolites

Gut microbiota and colorectal cancer (CRC)

The intestines serve as the primary habitat for the gut microbiome and play a crucial role in promoting or inhibiting the development of intestinal tumours. The primary mechanism by which it exerts this influence is by affecting the progression of CRC through its metabolic products [8]. Sulfate-reducing bacteria, such as *Desulfovibrio*, can transform primary bile acids into secondary bile acids, such as lithocholic acid and deoxycholic acid, which are associated with carcinogenicity [6]. The enterotoxin fragilysin, which is secreted by *Bacteroides fragilis (B. fragilis)*, stimulates the expression of inflammatory factors, the growth-related oncogene-α, and the oncogene c-Myc, thereby promoting the progression of cancer in the intestines under chronic inflammatory stimulation [9]. Conversely, evidence has suggested that *Streptococcus gallolyticus* plays a role in promoting tumour activity in colon cells. When cocultured with *S. gallolyticus*, colon cells exhibit increased expression of β-catenin, c-Myc, and proliferating cell nuclear antigen, key transcription factors involved in cancer development [10]. The cell surface virulence factor *Fusobacterium* adhesin A (FadA), expressed by *Fusobacterium nucleatum (Fn)*, interacts with the E-cadherin/β-catenin pathway, resulting in the upregulation of expression of transcription factors, oncogenes, and inflammatory genes [11].

The potential of the gut microbiota to modulate cancer suppression has yet to be fully harnessed. Recent evidence has suggested that bacteria such as *Faecalibacterium prausnitzii* and *Eubacterium rectale* can participate in the fermentation process to produce butyric acid (BA), a short-chain fatty acid (SCFA) that has various cancer-preventing effects [12, 13]. First, BA can induce the expression of the cyclin-dependent kinase tumour-suppressor protein inhibitor 1 A (p21) gene, inhibit the activator protein-1 (AP-1) signalling pathway, and increase the phosphorylation of c-Fos and ERK1/2 [14, 15]. Second, BA is utilised by colon cell mitochondria, assisting in the maintenance of cellular homeostasis and promoting the proliferation of colonic epithelial cells [16]. Third, GPR109a, an SCFA receptor expressed on immune cells, primarily activates BA-associated ligands and inhibits inflammatory cytokines, thereby suppressing the inflammatory process [17]. The host immune response combats DNA methylation-mediated GPR109a expression silencing through IFNγ signalling, thereby promoting anticarcinogenic effects [18].

Gut microbiota and gastric cancer (GC)

Within the realm of GC research, *Helicobacter pylori* (*H. pylori*) has emerged as the gut microbe with the strongest association with this disease, as recognised by the academic community. The bacterium orchestrates an array of immune and inflammatory responses by secreting virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), which disrupt numerous cellular signalling pathways [19]. Patients infected with CagA-positive *H. pylori* demonstrate elevated levels of inflammatory cytokines (such as IFNγ, TNF-α, IL-1, IL-1β, and IL-6) and activation of signalling pathways, including the ERK/MAPK, PI3K/Akt, NF-κB, Wnt/β-catenin, and STAT3 pathways, increasing their GC risk relative to that of uninfected patients. VacA-positive strains of *H. pylori* induce autophagy, particularly by targeting mitochondria, and manipulate critical cell growth and differentiation pathways, such as by upregulating MAP kinase and ERK1/2 expression, subsequently stimulating vascular endothelial growth factor activity and engaging the Wnt/β-catenin pathway while

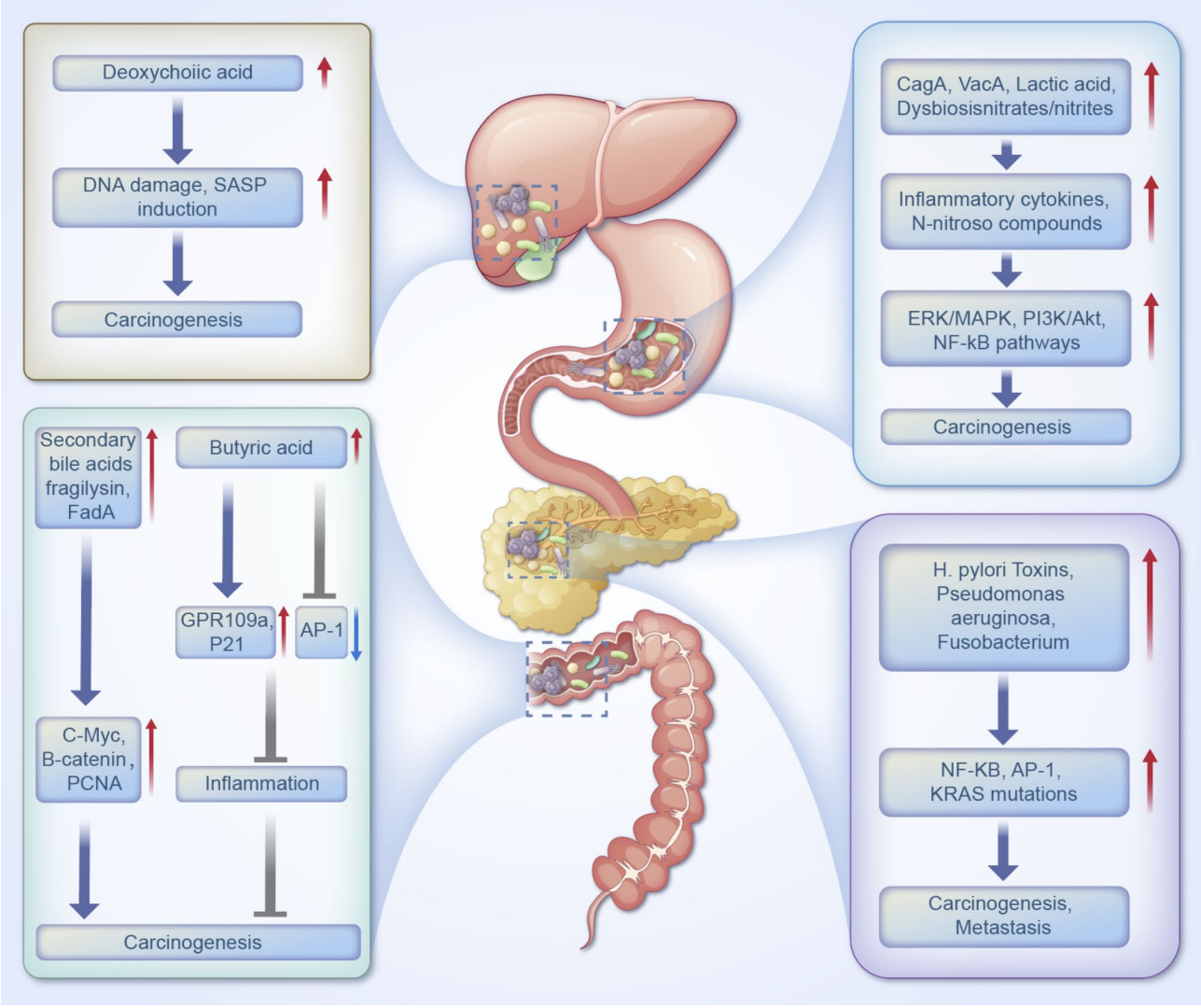

Fig. 1 The intricate interactions between the gut microbiota and cancer development. Deoxycholic acid and secondary BAs, such as fragilysin and FadA, contribute to DNA damage, SASP induction, and the upregulation of expression of oncogenic markers such as c-Myc and β-catenin, promoting carcinogenesis. Butyric acid, while generally exerting anti-inflammatory effects via GPR109a and p21, can also enhance inflammation through the AP-1 pathway. Additionally, bacterial toxins from *H. pylori*, *P. aeruginosa*, and *Fusobacterium* trigger activation of inflammatory pathways (NF-κB, AP-1) and genetic mutations (KRAS), leading to cancer development and metastasis. This depiction highlights the multifaceted role of the microbiota in carcinogenesis through various molecular mechanisms. Abbreviations: SASP: Senescence-associated secretory phenotype; FadA: *Fusobacterium* adhesin A; PCNA: Proliferating cell nuclear antigen; p21: Cyclin-dependent kinase tumour-suppressor protein inhibitor 1 A; AP-1: Activator protein-1; CagA: Cytotoxin-associated gene A; VacA: Vacuolating cytotoxin A; *H. pylori: Helicobacter pylori*

inhibiting GSK3 expression through PI3K/Akt signalling [15]. Furthermore, *H. pylori* promotes CpG island methylation in key genes, such as E-cadherin and tumour suppressor genes, significantly increasing the risk of GC. Additionally, the impact of *H. pylori* extends to dysbiosis of the intestinal microbiota [20]. Infected individuals present increased abundances of *Proteobacteria*, *Spirochaetes*, and *Acidobacteria* and decreased abundances of *Actinobacteria*, *Bacteroidetes* and *Firmicutes*, which are recognised as risk factors for GC development. The gut microbiota in patients with GC is more diverse than that in healthy individuals. However, the connection between this microbial diversity and GC remains to be fully elucidated, necessitating further research on the functions and mechanisms of these intestinal microbes [21].

In addition to the impact of *H. pylori* on GC, other members of the gut microbiota also play important roles. The genera *Lactobacillus* and *Streptococcus* include lactic acid-producing microbes that theoretically support tumour progression; lactic acid can act as a substrate for tumour growth and angiogenesis [22]. These findings suggest a potential oncogenic role for these beneficial bacteria under certain pathological conditions. Furthermore, several members of the phylum *Nitrospirae* have

been implicated in nitrate and nitrite metabolic pathways. These microbes lead to the production of carcinogenic N-nitroso compounds that contribute to the development of GC [23]. This underscores the complex ecosystem within the gut microbiota, in which various microbial species affect cancer risk through distinct metabolic activities. The broader implications of such microbial interactions with host physiology underscore the necessity for comprehensive research regarding their precise roles and mechanisms in gastric carcinogenesis.

The gut microbiota and other cancers

Gut microbiota metabolites have been implicated in the progression of various cancers, primarily through the production of inflammatory mediators that can lead to oncogenesis-related inflammation or accelerate cancer progression. Microbial metabolites disrupt liver metabolic pathways and immune responses, such as the recognition of lipopolysaccharide (LPS) by Toll-like receptor 4 (TLR4) to activate Kupffer cells and stellate cells, thereby promoting hepatocellular carcinoma (HCC) through inflammatory and oncogenic pathways, whereas *H. pylori*-associated VacA, CagA, and LPS further contribute to HCC by increasing IL-8 and TGF-β1 levels. However, the role of the intestinal microbiota and TLR4 activity in HCC initiation remains controversial. Deoxycholic acid derived from *Clostridium* causes DNA damage and induces a senescence-associated secretory phenotype (SASP) in hepatic stellate cells, involving inflammatory cytokines and growth factors and thereby contributing to inflammatory and obesity-associated HCC progression [15]. Pathogenic components of *H. pylori*, such as ammonia and LPS, along with increased levels of inflammatory cytokines, damage the pancreas by activating NF-κB and AP-1 signalling, leading to dysregulated cellular processes, KRAS gene mutations, and persistent STAT3 activation, together promoting pancreatic carcinogenesis and cancer progression. The presence of *Pseudomonas aeruginosa* can promote pancreatic cancer cell metastasis via Taste receptor 2 member 38 receptor signalling, whereas the presence of *Fusobacterium* spp., which are present in some pancreatic cancer tissues, is associated with poor prognosis [24]. The gut microbiota significantly influences the development and progression of various cancers, including CRC, GC, and others, through diverse mechanisms involving metabolic products, inflammatory responses, and interactions with host cellular pathways; both tumour-promoting and tumour-suppressing effects have been observed (Fig. 1; Table 1).

The gut microbiota induces alterations in the tumour immune microenvironment responses to tumours

The gut microbiota influences cancer progression by modulating T cell activity

Over the past several decades, numerous studies have shown the clear relevance of the microbiota and the TME through various associations. In particular, T cells are crucial components of the adaptive immune system, and their proper activation and differentiation are essential for tumour immunosurveillance [25]. *Fn* is a common oral anaerobic gram-negative bacterium found in many

Table 1 Gut microbiota involvement in tumour progression

Cancer Type	Gut microbiota	Prognosis/Outcome	Reference
Colon Cancer (CRC)	*Sulfate-reducing bacteria*, *Desulfovibrio*	Promotes CRC through secondary BAs (lithocholic acid, deoxycholic acid)	[6]
	Bacteroides fragilis	Promotes CRC via fragilysin, c-Myc expression	[9]
	Streptococcus gallolyticus	Promotes CRC via β-catenin, c-Myc, PCNA expression	[10]
	Fusobacterium nucleatum	Promotes CRC via FadA, E-cadherin/β-catenin pathway	[11]
	Faecalibacterium prausnitzii	Suppresses CRC via butyric acid production	[12]
	Eubacterium rectale	Suppresses CRC via butyric acid production	[13]
Gastric Cancer (GC)	*Helicobacter pylori* (CagA-positive)	Increases GC risk via inflammatory cytokines, various pathways	[15]
	Helicobacter pylori (VacA-positive)	Increases GC risk via autophagy, various pathways	[15]
	Helicobacter pylori	Promotes CpG island methylation, increases GC risk	[20]
		Causes dysbiosis, increases GC risk	[20]
		Increases abundance of *Proteobacteria*, *Spirochaetes*, decreases abundance of *Actinobacteria*, GC risk	[21]
	Lactobacillus and *Streptococcus*	Potentially oncogenic via lactic acid	[22]
	Nitrospirae	Carcinogenic via N-nitroso compounds production	[23]
Hepatocellular Carcinoma (HCC)	*Helicobacter pylori*	Contributes to HCC via VacA, CagA, LPS	[15]
	Clostridium	Promotes HCC via deoxycholic acid, inflammatory cytokines	[15]
Pancreatic cancer	*Helicobacter pylori*	Contributes to pancreatic cancer via ammonia, LPS	[24]
		Damages pancreas, promotes cancer via inflammatory cytokines	[24]
	Pseudomonas aeruginosa	Promotes pancreatic cancer metastasis via T2R38 receptor	[24]
	Fusobacterium species	Poor prognosis in pancreatic cancer	[24]

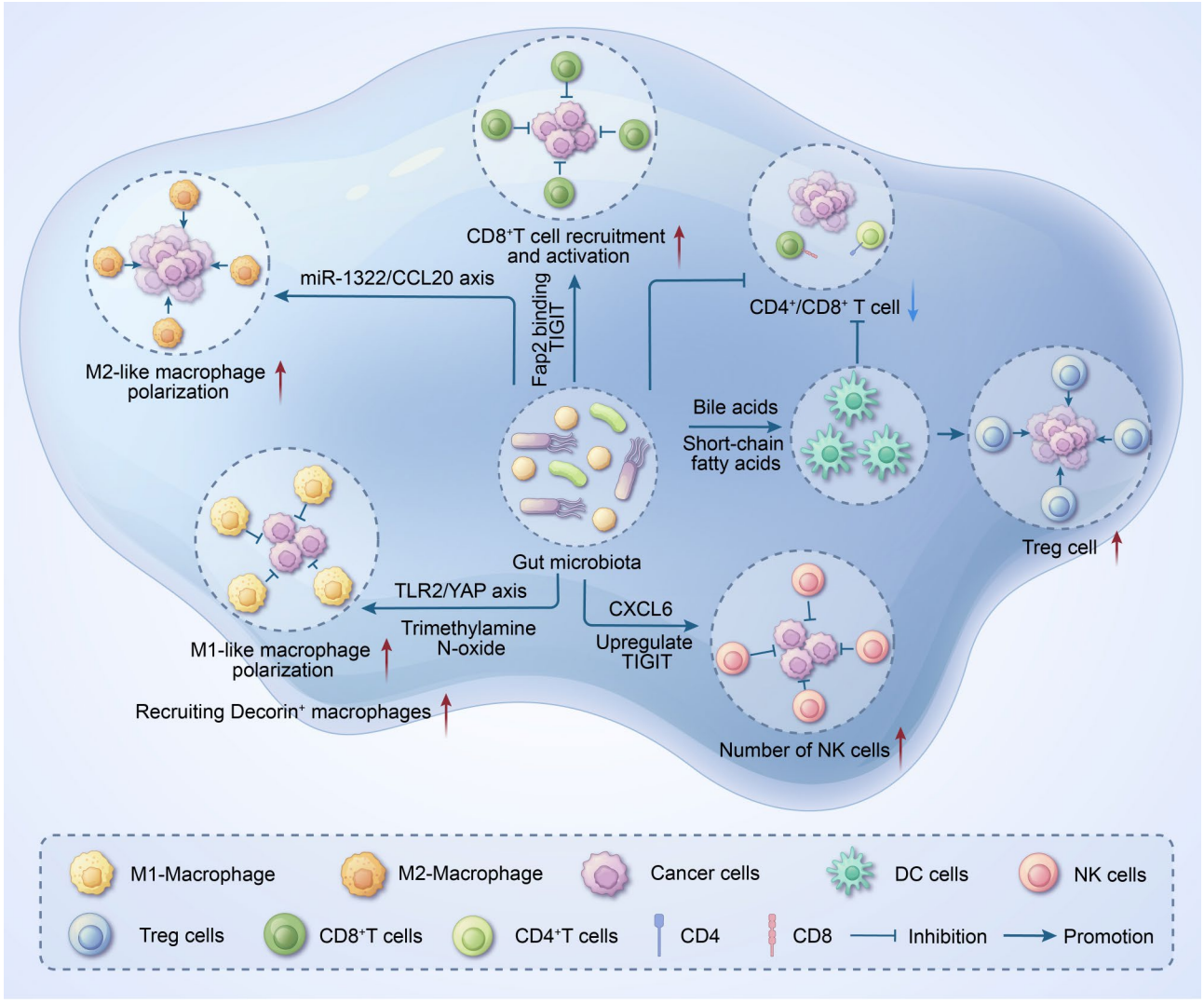

Fig. 2 The gut microbiota significantly influences the tumour immune microenvironment by modulating various immune cells. The gut microbiota affects T cell activity, promotes $CD8^+$ T cell recruitment, and can inhibit $CD4^+$ and $CD8^+$ T cells through mechanisms such as the fusobacterial Fap2 protein binding to TIGIT. The gut microbiota also directs macrophage polarisation, with imbalances leading to M2-like polarisation and certain metabolites promoting M1-like polarisation. Additionally, it impacts DCs and NK cells, enhancing antitumour responses by modulating their functions and interactions within the TME. Overall, these interactions shape the body's immune response to cancer and influence therapeutic outcomes. Abbreviations: CCL20: C-C motif chemokine ligand 20; Fap2: Fibroblast activation protein-2; TLR2: Toll-like receptor 2; YAP: Yes-associated protein 1; CXCL6: C-X-C motif chemokine ligand 6; NK cell: Natural killer cell; Treg cell: Regulatory T cell; TIGIT: T cell immunoreceptor with Ig and ITIM domains

tumours, especially in CRC, and it inhibits the function of $CD4^+$ and $CD8^+$ T cells by directly binding T cell immunoreceptor with Ig and ITIM domains (TIGIT), an inhibitory receptor expressed on the majority of human tumour-infiltrating leukocytes (TILs), via the *fusobacterial* fibroblast activation protein-2 (Fap2) [26]. *H. pylori* induces the development of GC, mediated mainly by CagA and VacA expression [27]. A recent study revealed that *H. pylori* infection can shift the immune response during the chronic inflammatory phase by replacing CagA-specific gastric $CD8^+$ T cells with $CD4^+$ T cells and changing the tissue-resident memory phenotype of CagA-specific $CD8^+$ T cells [28]. Moreover, *H. pylori* can induce the expression of programmed death ligand 1 (PD-L1) in gastric epithelial cells via the sonic hedgehog signalling pathway. These changes may help Hp-infected cells escape immunosurveillance and progress to GC cells [29]. Indeed, human clinical cohort studies have shown that *H. pylori* seropositivity is associated with decreased survival in non-small cell lung cancer patients receiving anti-programmed cell death protein 1 (anti-PD-1) therapy, largely due to a decreased number and activation status of tumour-specific $CD8^+$ T cells [30].

Recent studies have demonstrated that certain bacteria can suppress cancer cells by promoting T-cell activation, and their absence or downregulation may in turn

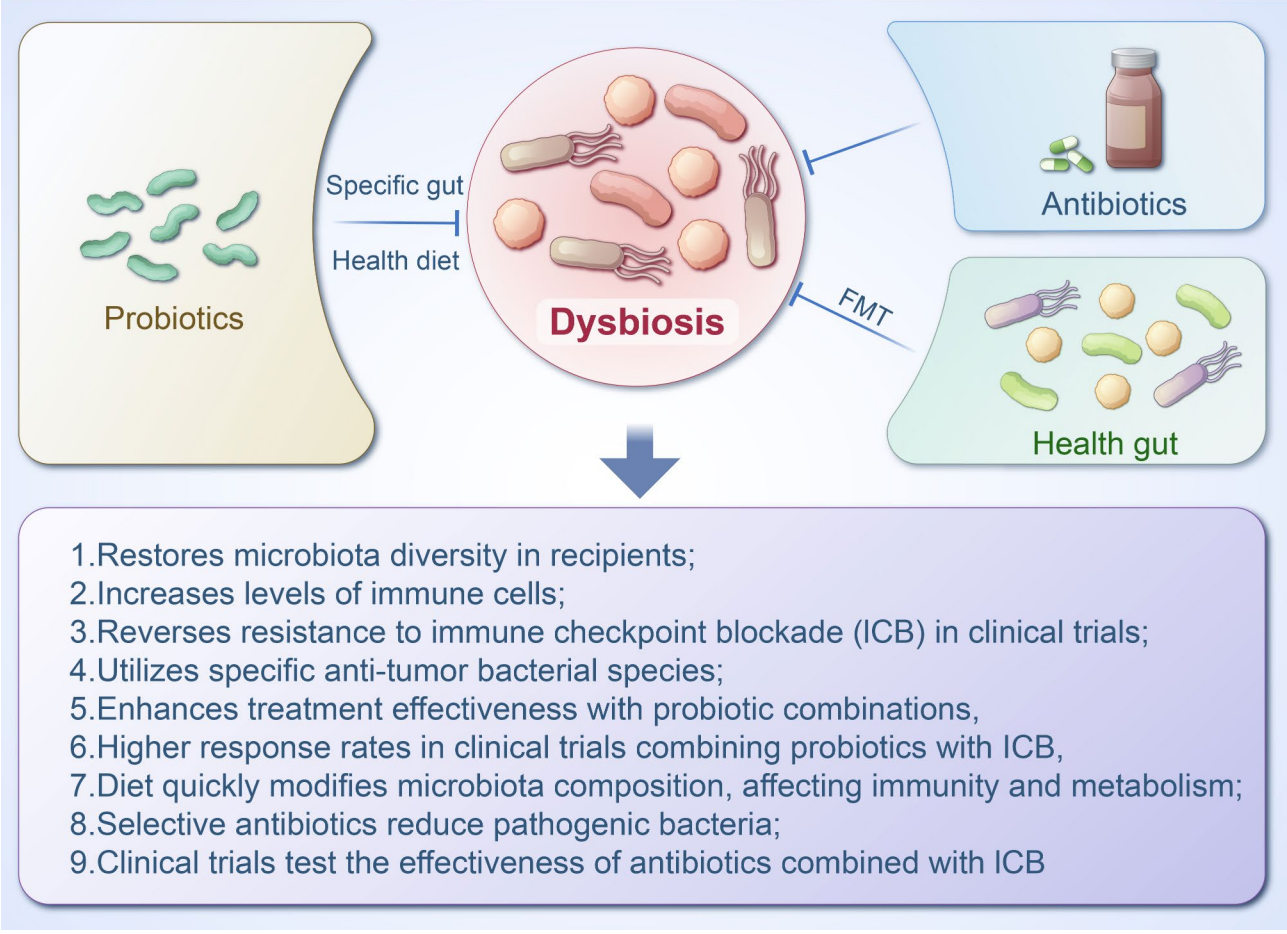

Fig. 3 Strategies to combat gut dysbiosis and their benefits. Dysbiosis, an imbalance in the gut microbiota, can be addressed using probiotics, a specific gut-health diet, FMT, and select antibiotics. These interventions aim to restore microbial diversity, increase immune cell numbers, reverse resistance to immune checkpoint blockade (ICB) in clinical trials, and utilise specific antitumour bacterial species. Additionally, combining probiotics with treatment enhances their effectiveness; dietary changes rapidly modify microbiota composition; and selective antibiotics reduce pathogenic bacteria. Clinical trials are also beng performed to evaluate the combined effectiveness of antibiotics and ICB treatments. Abbreviations FMT: Faecal microbiota transplantation

lead to cancer initiation. The administration of broad-spectrum antibiotics reduces the effectiveness of immune checkpoint inhibitors (ICIs) that target cytotoxic T lymphocyte-associated protein 4 or PD-1/PD-L1 [31–33], providing preclinical evidence that the abundance of some gut microorganisms may promote T-cell activation. Moreover, *Saccharopolyspora*, *Pseudoxanthomonas*, and *Streptomyces* have been reported to promote the recruitment and activation of $CD8^+$ T cells, which may contribute to antitumour immune responses [34]. As the gut microbiota can promote the maturation of lymphoid organs and the differentiation of immune cells, a recent study also suggested that the microbiota can increase the formation of tertiary lymphoid structures (TLSs) within the TME, which are positive prognostic markers for many types of solid tumours [35, 36]. In a murine model of CRC, introducing *Helicobacter hepaticus* (*H. hepaticus*) resulted in a decreased tumour load by triggering the formation of classic TLSs containing germinal centres. Notably, these conventional TLSs housed both *H. hepaticus* and follicular helper T cells specific to *H. hepaticus*. This finding implies that within a tumour, *H. hepaticus* acts as a central focus for the TLS-mediated antitumour immune response [37].

The gut microbiota influences cancer progression by directing macrophage polarisation

Tumour-associated macrophages (TAMs), comprising resident macrophages and circulating monocytes recruited to the TME, have been recognised as key inflammatory cells in the TME [38]. The correlation of TAMs with the prognosis of cancer patients is believed to stem from the heterogeneity of TAMs in both inter- and intratumoural contexts [39]. To delineate the diverse roles of TAMs under various conditions, they are generally categorised into M1-like and M2-like subtypes [40]. M1-like macrophages are activated to promote type 1 helper T (Th1) cell immune responses by producing type

1 proinflammatory cytokines (such as IL-1β, IL-1α, and IL-6), suppress tumour progression, and inhibit type 2 helper T (Th2) responses. In contrast, M2-like macrophages contribute to extracellular matrix production and anti-inflammatory effects, including producing IL-4 and IL-10, which are involved in Th2 immune responses, wound healing promotion, and Th1 response inhibition [41]. The interactions between the gut microbiota and its related products in the TME could lead to diverse changes in tumour progression and prognosis through their interplay with TAMs.

In CRC patients, gut microbiota imbalance promotes high expression of the secretory protein cathepsin K, leading to tumour cells stimulating M2-like macrophage polarisation to induce CRC invasion and metastasis [42]. *Fn* is a type of human intestinal flora that has been shown to induce M2-like macrophage polarisation and promote CRC metastasis via the miR-1322/CCL20 axis [43]. *Peptostreptococcus anaerobius* is an anaerobic bacterium that specifically adheres to the mucosa of CRC patients. Although the underlying mechanism is unknown, analyses of tumour-infiltrating immune cell populations have shown that *P. anaerobius* can increase the number of immune cells, including TAMs, to promote tumour progression [44]. On the other hand, *Firmicutes* has been shown to have antitumorigenic effects in response to macrophage depletion [45]. *Bifidobacterium adolescentis* inhibits colorectal tumorigenesis by recruiting and facilitating the infiltration of decorin$^+$ macrophages via the activation of Toll-like receptor 2 (TLR2) and regulation of both primary human macrophages and M1 macrophages through the TLR2/YAP axis [46].

In GC patients, alterations in immune responses and immune evasion by *H. pylori* are intricately connected with the presence of TAMs [47]. The interaction between *H. pylori* and macrophages in the TME predominantly involves the induction of M2-like macrophage polarisation, diminishing antigen presentation capabilities, and modulating macrophage secretion factors, collectively fostering the progression and invasion of GC [48]. *Propionibacterium acnes* triggers M2 polarisation of macrophages via TLR4/PI3K/Akt signalling to promote the migration of GC cells [49].

Some oral-gut microbiota have been found to promote miR-21 expression and reduce the expression of phosphatase and tensin homologues (well-known tumour suppressors), and their loss can induce M2-like macrophage polarisation leading to immune escape by pancreatic ductal adenocarcinoma (PDAC) [50]. In contrast, the gut microbiota metabolic product trimethylamine N-oxide, which has been shown to increase the secretion of the proinflammatory cytokines IL-6 and IL-12p4, leads to the inhibition of PDAC cells after inducing macrophage polarisation towards an M1-like phenotype [51]. In addition, under the influence of *Lactobacillus casei* and *Lactobacillus reuteri*, TLR4 is inhibited, promoting M1-like macrophage polarisation, to alleviate PDAC and regulate gut microbial homeostasis [52].

Tumour cells overexpressing antiphagocytic surface proteins such as CD47 and CD24 (known as "do not eat me" signals) are able to evade macrophages [53]. Agents antagonising these "do not eat me" proteins and inducing interactions between tumour cells and macrophages have shown therapeutic potential in patients with various cancers [54]. Therefore, the role of macrophages in tumour treatment is crucial and should not be overlooked.

The gut microbiota and other immune cells in the TME

In the TME, in addition to the primary roles of T cells and macrophages, dendritic cells (DCs) and natural killer (NK) cells also contribute to tumour progression. This summary provides an overview of the gut microbiota and its interactions within the TME.

Secondary BAs, metabolic products of gut microbiota dysbiosis in intestinal tumours, activate the TGR5 receptor, thereby inhibiting NF-κB activation in DCs via the cAMP−protein kinase A pathway. This inhibition leads to the secretion of inflammatory factors expressed in T cells, thereby inducing T cell differentiation [55]. The presence of SCFAs impairs the ability of DCs to induce the proliferation of CD4$^+$ and CD8$^+$ T cells, potentially owing to the upregulation of IL-10 expression in DCs. Additionally, SCFA-treated DCs have been reported to promote regulatory T cell function while inhibiting effector T cell responses [56]. These results suggest that gut microbiota dysbiosis can enhance tumour cell immune evasion by affecting DC functionality. In addition, in a tumour model of mice colonised with *H. hepaticus*, an improved cancer prognosis was observed, along with an increased number of NK cells in the tumour tissue [37]. These findings suggest that NK cells may exert their tumour-killing functions following modulation by the gut microbiota and that the gut microbiota-mediated conversion of primary BAs to secondary BAs can regulate the expression of CXCL16 (C-X-C motif chemokine ligand 16) in liver sinusoidal endothelial cells, thereby promoting the accumulation of NK cells and increasing IFNγ production to exert antitumour effects [57]. Clinical studies have also shown that in tumour patients positive for *Enterobacter* and *Enterobacteriaceae*, the immune receptor TIGIT has significantly upregulated expression in NK cells, leading to sustained clinical benefits [58].

The interactions between the gut microbiota and the tumour immune microenvironment significantly influence cancer progression by modulating T cell activity, directing macrophage polarisation, and affecting the functions of other immune cells, thereby shaping the

body's immune responses against tumours and impacting therapeutic outcomes (Fig. 2).

Modification of the gut microbiota as cancer therapy

Given that gut and tumour microbiota have been demonstrated to play key roles in cancer development, they are anticipated to become crucial intervention strategies in cancer therapy along with enhancing current therapeutic approaches through targeted reconstruction. Various strategies, such as faecal microbiota transplantation (FMT), targeted microbial therapies, dietary interventions, and phage-based approaches, are being explored in clinical trials to treat, intercept, and prevent cancer.

Faecal microbial transplantation (FMT)

FMT can result in healthier and more diverse microbiota than can a patient's own preconditioning microbiota, and it has been shown to be safe and effective for restoring microbiota diversity in recipients [59]. Moreover, recipients of autologous FMT exhibit increased numbers of various types of white blood cells, indicating the potential benefits of FMT [60]. Nonetheless, the potential danger of transmitting pathogens or antibiotic-resistant bacteria to immunosuppressed recipients underscores the importance of preserving a patient's own microbiota.

FMT represents an initial approach for modulating gut microbiota and has been investigated in clinical trials in combination with immune checkpoint blockade (ICB) [31, 33, 61–63]. It has shown promise for reversing resistance to ICB therapy, with two recent clinical trials demonstrating its ability to restore the ICB response in melanoma patients resistant to treatment [64, 65]. Successful colonisation of the recipient gut by the donor microbiota, particularly bacteria such as *Ruminococcaceae* and *Bifidobacteriaceae*, has been associated with increased immune infiltration in tumours and enriched therapy-associated serum metabolites [64, 65]. Although the pilot studies were small and single-armed, they demonstrated a 36% overall clinical response, which is higher than that observed with other combined treatments for patients resistant to anti-PD1 therapy, and the treatment did not result in additional severe toxicity [64, 65]. Furthermore, even when administered via a single colonoscopy without antibiotic conditioning, FMT altered the microbiota composition for more than a year [64]. Currently, trials are underway to test similar approaches in CRC patients (NCT04729322 and NCT04130763).

Research is now focused on determining whether an ideal FMT donor for cancer trials is a successful cancer responder or healthy individual. Clinical trials investigating a combination of ICB treatment with FMT in complete responders or healthy donors are underway and have shown promising early results. FMT has also shown efficacy beyond ICB treatment, particularly in managing steroid-refractory gastrointestinal graft-versus-host disease after haematopoietic stem cell transplantation. Although FMT trials face challenges, including donor selection and administration protocols [66, 67], they provide valuable insights for developing more effective microbiome-based strategies for cancer treatment and beyond.

Probiotics and microbial consortia

The earliest form of immunotherapy utilised microbial species as antitumour agents. As some bacterial species show proinflammatory properties or the capacity to infiltrate and thrive in a hypoxic TME, they have been used as antitumour agents [68], such as *Lactobacillus* spp. and *Bifidobacterium* spp [69]. , *Blautia producta* [70], *Clostridium scindens* [71] and *Clostridium* spp [72]. , which have been reported to have anti-inflammatory or antitumour properties in both patient and mouse models. In certain instances, these bacteria have been genetically engineered to enhance their anticancer efficacy or to serve as a vehicle for delivering tumour-toxic substances [73].

In contrast to FMT, current efforts to modulate the gut microbiota are focused on transplanting specific microbial species or designer microbial consortia to improve patient response to ICB and other cancer treatments. In mouse models, specific gut bacteria such as *Akkermansia muciniphila (A. muciniphila)* [31], *B. fragilis* [74], *Bifidobacterium* [33], *Lactobacillus rhamnosus GG* [75], *Lacticaseibacillus paracasei* [76], or combinations of probiotics [77, 78] have been shown to enhance the effectiveness of ICB. In a small, open-label trial, patients with metastatic renal cell carcinoma (RCC) who received CBM588 (containing *C. butyricum*) alongside ICB had a greater response rate and increased progression-free survival than did those who received ICB alone, suggesting that the addition of bifidogenic bacterial products can enhance clinical outcomes in RCC patients [79]. Although individual probiotic strains have shown potential, bacterial consortia may be more effective for maintaining an ecological balance within the gut microbiota. For example, the oral administration of four *Clostridiales* strain combinations (*Roseburia intestinalis*, *Eubacterium hallii*, *F. prausnitzii*, and *Anaerostipes caccae*) to mice increased the number of activated $CD8^+$ T cells within tumours and effectively treated both chemically induced and transplanted colorectal tumours [80]. Another study revealed that the probiotic combination Prohep lowered Th17 (helper T 17) cell numbers in tumours, thereby slowing HCC progression in mice [81]. Some clinical trials have tested the therapeutic potential of the probiotic combination VSL#3 in patients with nonalcoholic fatty liver disease [82] or cirrhosis [83] and have shown that

administration of probiotics alleviates the severity of these conditions, which are closely linked to the development of HCC.

Despite the initial success observed, the feasibility and efficacy of this approach remain understudied. Several trials are currently underway to evaluate the therapeutic potential of microbial consortia or targeted microbial strategies in combination with existing cancer treatments (NCT03686202 and NCT05079503). Nevertheless, such approaches have shown significant efficacy in noncancer conditions such as *Clostridium difficile*-related colitis and are expected to offer distinct advantages over FMT in long-term efforts to optimise gut microbiota modulation for cancer treatment.

Diet and prebiotic strategies

Apart from the aforementioned direct strategies for modulating the gut microbiota, diet plays a crucial role in regulating microbial composition and function. Changes in the diet quickly modify the composition of the gut microbiota and affect the production of bacterial metabolites derived from food fermentation, leading to significant metabolic and immunological consequences [84]. Researchers have tested various dietary strategies, such as high-fibre diets [85, 86], ketogenic diets [87], caloric restriction [88, 89], intermittent fasting, fasting-mimicking diets [90], and fermented foods [84], in both mice and patients to improve cancer treatment [91]. In some cases, these approaches influence immunity by changing the composition of the gut microbiota. These studies are pivotal, as they offer a viable approach to modulate the function of gut microorganisms, either alongside other microorganism-targeting strategies or in conjunction with alternative cancer treatments.

In a mouse model, a low-fibre diet al.tered the microbiota and decreased the abundance of *Bifidobacterium* spp [85]. and increased the abundance of *A. muciniphila* [92], leading to a poor response to anti-PD1 therapy. Germ-free mice did not show differential responses based on fibre intake, indicating that dietary fibre affects anticancer immunity through changes in the microbiota [85]. A high-fibre diet in mice promotes tumour immunity by supporting fibre-fermenting *Ruminococcaceae* spp., which enhances the activation and infiltration of T cells, including ICOS-expressing $CD8^+$ and $CD4^+$ T cells, into tumours [85]. Patients with melanoma undergoing anti-PD1 therapy have better response and survival rates on a fibre-rich diet of more than 20 g fibre/day, with each additional 5 g of fibre reducing the risk of progression or death by 30%[85].

Furthermore, there are significant opportunities to leverage prebiotics in cancer treatment. Prebiotics, such as inulin and pectin, are soluble fibres that are naturally present in many vegetables and fruits. The administration of prebiotics enhances the effectiveness of anti-PD-1 antibodies in various mouse models [93]. Mechanistically, although prebiotics cannot be digested by gastrointestinal enzymes, they can be fermented by bacteria, further modifying the composition of the gut microbiota (such as enriching the abundance of *Ruminococcaceae* spp. and of individual bacteria such as *A. muciniphila*) and their metabolites (such as SCFAs and cyclic diadenosine monophosphate (cyclic di-AMP)), reinforcing the mucosal barrier, improving epithelial integrity, and regulating the activity of innate immune cells to induce antitumour immunity [94, 95]. These effects of prebiotics can be harnessed for therapeutic potential [96].

Specific bacterial depletion by targeted antibiotics or other methods

Long-term use of broad-spectrum antibiotics has been linked to significant alterations in the gut microbiota and poorer outcomes according to some studies [97, 98]. The median survival of patients who received antibiotics before or immediately after anti-PD-1 therapy was nearly half that of those who did not [31]. Additionally, patients with advanced cancer who received antibiotics before or after immune ICB therapy experienced lower response rates and shorter overall survival and progression-free survival [97, 99]. In general, the use of antibiotics can lead to significant alterations in the composition of the gut microbiota, potentially exerting conflicting effects on the ICB response. Therefore, carefully selected antibiotic regimens can indirectly exert anticancer effects and reduce complications during cancer treatment by targeting oncogenic or pathogenic microorganisms [100–102]. More specific antibiotics that modulate the gut microbiota and those of other niches may prove beneficial for cancer patients and disease management.

For example, dietary heme, a metabolite derived from red meat, can induce cytotoxicity in colonic contents, promoting compensatory hyperproliferation and hyperplasia of the epithelium and thereby increasing the risk of CRC. Antibiotics such as ampicillin, metronidazole, and neomycin can mitigate this risk by strengthening the mucus barrier and epithelial integrity [103]. Vancomycin inhibits the growth of primary and metastatic liver cancer in mice by promoting the migration of NKT cells and increasing the production of IFN-γ in the liver [57], leading to the depletion of gram-positive bacteria, especially *C. scindens* [99]. A clinical trial (NCT03785210) is being undertaken to investigate whether vancomycin enhances the effectiveness of anti-PD1 therapy in patients with primary liver cancer or metastases.

In recent years, to minimise disruption of the commensal microbiota and ensure effective cancer treatment, novel technologies, such as the CRISPR–Cas9 system, which is delivered by phages [104, 105] and targets

specific bacteria at the microbiome–cancer interface, are essential. An example of this is the CRISPR–Cas9 system, which enables precise genetic alterations and could provide targeted therapies without disrupting the microbiota [106]. Notably, the administration of irinotecan-loaded dextran nanoparticles covalently linked to azide-modified phages, which target *Fn* in tumours, enhances the efficacy of chemotherapy against CRC [107]. These approaches are anticipated to proliferate in the future and will have a considerable impact on the therapeutic landscape as this field progresses.

Modulation of the gut microbiota is a promising strategy for cancer therapy. FMT and administration of probiotics enhance the immune response and therapeutic effectiveness in various cancers, such as melanoma, CRC, and RCC (Fig. 3; Table 2). Dietary interventions and prebiotics improve the gut microbiota composition, boosting antitumour immunity. Targeted antibiotics and CRISPR-Cas9 offer precise bacterial depletion, further enhancing treatment outcomes. These approaches highlight the critical role of the gut microbiota in cancer therapy optimisation.

Conclusions and future perspectives

The intricate relationship between the gut microbiota and immune cells within the TME has opened new avenues for cancer therapy. Recent research has demonstrated that the gut microbiota significantly affects tumour progression and therapeutic responses by modulating immune cell functions through its metabolic products. For example, the conversion of primary BAs to secondary BAs can regulate immune cell activity and enhance antitumour responses, whereas dysbiosis can lead to immune evasion by tumour cells [6, 55, 57, 108].

Emerging therapeutic strategies such as FMT, administration of probiotics, dietary interventions, and administration of targeted antibiotics show promise in modulating the gut microbiota to improve cancer treatment outcomes. The aim of these approaches is to restore microbial balance, enhance immune cell functionality, and potentially reverse resistance to immunotherapy. Clinical studies have begun to validate these strategies, highlighting their potential to increase the effectiveness of existing cancer treatments.

Gut microbiota dysbiosis can impact energy metabolism, immune homeostasis, gut defence mechanisms, organic compounds, vitamin production, and abnormal hormone regulation [109, 110]. Dysbiosis is also associated with various cancers. This understanding has led to

Table 2 Gut microbiota involvement in cancer therapy

Cancer type	Microbiota species	Treatment method	Description and outcomes	Refer
Melanoma	*Ruminococcaceae*, *Bifidobacteriaceae*	Faecal Microbiota Transplantation (FMT)	Increased immune cell infiltration, improved ICB therapy resistance, 36% overall clinical response rate, no additional severe toxicities.	[64, 65]
Colorectal Cancer (CRC)	*Fusobacterium nucleatum*, *Bifidobacterium*, *Lactobacillus*, *Ruminococcaceae*, *Akkermansia muciniphila*	FMT, Specific Bacteria Depletion (e.g., antibiotics), Probiotics and Microbial Consortia (e.g., high-fibre diet and prebiotics)	FMT alters gut microbiota, probiotics improve ICB efficacy, high-fibre diet enhances antitumour immunity, antibiotics and CRISPR-Cas9 target specific oncogenic bacteria.	[31, 33, 69–72, 75, 76]
Gastric Cancer (GC)	*Helicobacter pylori*, *Propionibacterium acnes*	FMT, Specific Bacteria Depletion (e.g., antibiotics), Probiotics and Microbial Consortia (e.g., high-fibre diet and prebiotics)	FMT improves immune cell infiltration and treatment-related metabolite abundance, probiotics and prebiotics enhance immune response, antibiotics target *H. pylori* to reduce tumour progression.	[48, 49]
Pancreatic Cancer (PDAC)	*Saccharopolyspora*, *Pseudoxanthomonas*, *Streptomyces*, *Lactobacillus casei*, *Lactobacillus reuteri*	FMT, Specific Bacteria Depletion (e.g., antibiotics), Probiotics and Microbial Consortia (e.g., high-fibre diet and prebiotics)	FMT promotes $CD8^+$T cell activation, probiotics and prebiotics enhance antitumour immunity, antibiotics modulate microbiota to enhance treatment efficacy.	[34, 52]
Liver Cancer (HCC)	*Blautia producta*, *Clostridium scindens*, *Bifidobacterium*, *Lactobacillus*, *Roseburia intestinalis*	FMT, Specific Bacteria Depletion (e.g., antibiotics), Probiotics and Microbial Consortia (e.g., high-fibre diet and prebiotics)	FMT improves graft-versus-host disease, probiotics and prebiotics modulate Th17 cell levels, slow tumour progression, antibiotics promote NK cell migration and IFN-γ production to enhance antitumour response.	[66, 67, 69, 70, 80, 99]
Renal Cell Carcinoma (RCC)	*Clostridium butyricum*	Probiotics and Microbial Consortia (e.g., high-fibre diet and prebiotics)	CBM588 combined with ICB increases response rate and progression-free survival (PFS), probiotics improve clinical outcomes.	[79]
Nonalcoholic Fatty Liver Disease	*VSL#3 (Probiotic combination)*	Probiotics and Microbial Consortia	Probiotics alleviate disease severity, improve conditions related to HCC development.	[82, 83]

rapid growth in research exploring the clinical potential of regulating the gut microbiota. Numerous studies have investigated the treatment of various cancers through dietary therapy, prebiotics, probiotics, and even FMT, and significant progress has been made, as discussed above. Given that bacterial abundance is significantly elevated in GC patients, bacterial overgrowth in the stomach could be a potential marker for GC [111]. For example, the potential utility of some specific microbial signatures for the early detection and screening of CRC has been identified, and some specific species, such as *A. halli*, *C. difficile*, and *Fn*, serve as specific markers for excess body weight-related CRC [112, 113]. These findings contribute to enhancing the accuracy of GC diagnosis and treatment.

For the diagnosis and treatment of different patients, monitoring the gut microbiota can improve the accuracy of early disease detection. Owing to the ease of sample collection, patient compliance and participation can be greatly improved, and the role of the gut microbiota can significantly reduce the side effects of treatment. Personalised treatment can be achieved by targeting the specific diversity of the gut microbiota in a patient, not only reducing medical costs but also improving treatment efficacy, making it a highly promising therapeutic approach. Future research should focus more on unlocking the potential of the gut microbiota, which could lead to more effective and personalised approaches for disease treatment.

Technological variations are also key factors contributing to the inconsistent results observed in microbiome-related studies [114]. 16 S rRNA sequencing can be used to map the microbiome but is affected by various factors, such as sample collection, contamination, and analysis methods, making comparisons between studies difficult. It is unclear whether the detected genes are from live microbes, and contamination remains a challenge. Studying the microbiota directly in gastric biopsies could provide clearer insights into their true presence and abundance in the stomach. Emerging technologies and methodologies are expanding our understanding of the interactions between the gut microbiota and the TME. For example, whole-metagenome sequencing could enhance the detection of bacterial species, including rare ones, and this technique uses bioinformatics to identify microbial targets that could distinguish chronic gastritis from GC [115]. Owing to high background noise from host RNA, traditional metatranscriptomic methods struggle with these low-microbial samples. To address this, a new workflow combining Kraken 2/Bracken for taxonomic analysis and HUMAnN 3 for functional analysis was developed and tested in one study. The approach to this study was validated via synthetic samples and human gastric tissues, demonstrating its ability to accurately identify microbial species and functions with minimal false positives. This method could enhance understanding of the microbiome in mucosal tissues and its interactions with the host in both health and disease [116].

Recent advancements also aim to minimise disruption of the commensal microbiota while enhancing the effectiveness of cancer treatment. One such technology is the CRISPR–Cas9 system, which allows for precise genetic modifications, potentially offering targeted therapeutic approaches without adversely affecting the microbiota [106]. A new approach called "probiotic surface coating" technology has been proposed in recent years. This technique involves the use of single-cell coating technology to create a protective outer layer on probiotics, resulting in "armoured probiotics." By combining functional materials with probiotics based on key surface elements such as charge, adhesion factors, and inherent antigens, various biological and chemical methods have been employed. This technology aims to increase the survival and bioavailability of probiotics in the gastrointestinal tract or affected areas, reduce their biotoxicity and immune rejection, and precisely regulate their activity or biological behaviour, thereby improving the effectiveness of disease treatment [117]. Another novel method involving base editing of bacteria in the mouse gut has been reported. Editing the β-lactamase gene achieved 93% editing efficiency, and the modified bacteria persisted in the intestine for at least 42 days. This technique, which uses nonreplicating DNA vectors, prevents payload spread. This method was also used to edit therapeutic genes in *E. coli* and *Klebsiella pneumoniae* in vitro and to modify pathogenic genes in *E. coli* [118]. Future research should also focus on developing relevant animal models to demonstrate that these novel methods can achieve beneficial outcomes for patients.

The gut microbiota is a highly diverse and complex ecosystem composed of various microorganisms within the human intestinal tract, which is one of the most extensive interfaces. In recent decades, studies oregarding the gut microbiota have highlighted its essential role in supporting overall health and well-being. However, most of the studies are cross-sectional, scarce, and somewhat controversial; thus, they should be interpreted cautiously, particularly when considering causation. To evaluate potential causal relationships, it would be necessary to study bacterial colonisation and its fluctuations in relation to the development of GC longitudinally across different populations worldwide, including analysis of precancerous lesions, different regions in the stomach, and different types of GC. Recently, one study offered a comprehensive analysis of longitudinal multisite microbiome ecology and host dynamics. By utilising date-matched microbiome and host -omics data, we can not

only deepen our understanding of the stability and individuality of microbiomes across different body sites but also propose mechanism-generating hypotheses on host–microbiome interactions within the context of prediabetes [119]. Such research could illuminate the gradual development of microbial dysbiosis preceding GC. The recent advancements in the collection of longitudinal cohorts to study health effects may help address these more complex health questions. Indeed, investigations of longitudinal alterations in the gut mycobiome have revealed that certain gut fungi could serve as noninvasive biomarkers or potential treatments for liver disease progression, particularly from cirrhosis to HCC [120]. Another study investigated the link between changes in gut microbiota dysbiosis and the development of GC. They analysed bacterial DNA from stomach biopsies in a longitudinal study involving 43 participants over at least 5 years and reported that patients with early gastric neoplasia had higher abundance of certain bacteria, such as *Proteobacteria* and *H. pylori*, and lower abundance of others, such as *Bacteroidetes*. This study identified specific bacterial features and functions that could predict progression to EGN with significant accuracy, suggesting that monitoring the microbiome might help in the early detection of GC [121]. More studies are needed to focus on longitudinal analysis of the gut microbiome in the future.

In conclusion, the gut microbiota represents a critical and modifiable factor in cancer therapy. Continued exploration and understanding of its interactions with the immune system will pave the way for innovative treatments, offering hope for improved prognosis and quality of life for cancer patients.

Abbreviations

TME	The Tumour Microenvironment
CRC	Colorectal Cancer
B. fragilis	Bacteroides fragilis
SASP	Senescence-Associated Secretory Phenotype
Fn	Fusobacterium Nucleatum
FadA	Fusobacterium adhesin A
BA	Butyric Acid
SCFA	Short-Chain Fatty Acid
PCNA	Proliferating Cell Nuclear Antigen
p21	Cyclin-dependent kinase tumour-suppressor protein inhibitor 1 A
AP-1	Activator Protein-1
CagA	Cytotoxin-associated gene A
VacA	Vacuolating cytotoxin A
H. pylori	Helicobacter pylori
TLR4	Toll-Like Receptor 4
LPS	Lipopolysaccharides
HCC	Hepatocellular Carcinoma
TIGIT	T cell Immunoreceptor with Ig and ITIM domains
CCL20	C-C motif Chemokine Ligand 20
Fap2	Fibroblast activation protein-2
TLSs	Tertiary Lymphoid Structures
TLR2	Toll-Like Receptor 2
YAP	Yes-Associated Protein 1
CXCL6	C-X-C motif Chemokine Ligand 6
NK cell	Natural Killer cell
Treg cell	Regulatory T cell
FMT	Faecal microbiota transplantation
A. muciniphila	Akkermansia muciniphila
Th	T helper
RCC	Renal Cell Carcinoma
PDAC	Pancreatic Ductal Adenocarcinoma
E. coli	Escherichia coli

Supplementary Information

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Supplementary Material 1

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Author contributions

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Data availability

Not applicable.

Declarations

Conflict of interest

The authors have no potential conflicts of interest to disclose.

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