Gastrointestinal Cancers: What Is the Real Board of Microenvironment and the Role of Microbiota–Immunity Axis?

Edda Russo, Federico Boem, Lavinia Curini, and Amedeo Amedei

Abstract

The tumor microenvironment (TME) represents a complex and dynamic entity, able to affect oncogenesis, tumor cells' preservation, local invasion, and metastatic propagation of gastrointestinal cancers. The TME is able to change according to malignancy type, but common characteristics include immune cells, blood vessels, stromal cells, and extracellular matrix. Moreover, emerging evidence includes also the gut microbiome (GM) in the TME and, in particular, its mutual interplay with the immune response (named microbiome–immunity axis), in gastrointestinal cancers. In this scenario, the reciprocal interaction between cancer cells, immune system, and GM leads to new thinking on the TME borders' redefinition in the field of gastrointestinal cancers. In this chapter, we retraced the most important studies on the crosstalk between microbiome (and its metabolites) and immune response, and how it affects the TME of gastrointestinal cancers. We discussed the multiple layers of the TME within the holobiont vision and examined how microbial dysbiosis could influence the mutual relationship between the host immunology and GM in several districts of the gastrointestinal tract, affecting oncogenesis, tumor progression, and response to immunotherapy treatment. A deep understanding of all the actors and dynamics of TME in the gastrointestinal tract will allow the design of more effective and tailored therapies, able to target specific TME levels and components, associated with the malignancy development and progression.

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1 Introduction

Digestive tumors are malignant conditions of the gastrointestinal (GI) system and accessory digestion organs (esophagus, biliary system stomach, small intestine, large intestine, rectum, pancreas, and anus). The general symptoms can include obstruction, abnormal bleeding, and different associated problems. Gastrointestinal tract (GIT) cancers represent a significant portion of the global health-care burden (Arnold et al. 2020), and, according to their prevalence, colon (CRC), stomach, and liver cancers are the main concerns within this group (fourth, sixth, and seventh most prevalent, respectively). The principal causes of death are stomach cancer (second highest), liver cancer (third highest), and CRC (fifth highest) (Russo et al. 2019). Even though it is not one of the top 10 most common cancers, pancreatic ductal adenocarcinoma (PDAC) has some of the worst prognoses and is presumed to be one of the leading causes of death from cancer by 2030 (Rahib et al. 2014). Furthermore, esophageal cancer is common in some countries (Bray et al. 2018).

The multistep biological mechanisms acting in the prevention and development of GI cancer are still largely unknown, which is why GI cancers are thought to be a multifactorial disease caused by complex interactions between genetic factors, epigenetic changes, immune function, environment elements (including geographic area and socioeconomic status), way of life, and nutrition.

The majority of GI cancer investigations and therapeutic strategies have mainly concentrated on cell-autonomous processes in the epithelial compartment. Indeed, tumor cells trigger important molecular, cellular, and physical alteration within their host tissues. Nevertheless, there is mounting in vivo evidence that epithelial cells react to their "microenvironment." Indeed, the emerging tumor microenvironment (TME) represents an intricate and ever-changing entity. TME patterns vary according to malignancy type, but common characteristics include immune cells, blood vessels, stromal cells, and extracellular matrix (ECM). The TME is a dynamic "influencer" of tumor development; in fact, a mutual relationship is created between cancer cells and TME elements in early oncogenesis to promote tumor cell preservation, local invasion, and metastatic propagation. Moreover, the TME coordinates a molecular system that fosters angiogenesis, to re-establish oxygen/nutrient source and remove metabolic waste, in order to overcome a hypoxic and acidic microenvironment. In addition, cancers are infiltrated by a variety of adaptive and innate immune cells that can have both pro- and antitumorigenic impact (Anderson and Simon 2020). Finally, another critical feature of this complex network in GI cancers is the luminal content, particularly the gut microbiome (GM); its implications on immunity and tumorigenesis are only just beginning to be recognized (Fig. 1) (Russo et al. 2016). Nevertheless, all the abovementioned factors could influence GI

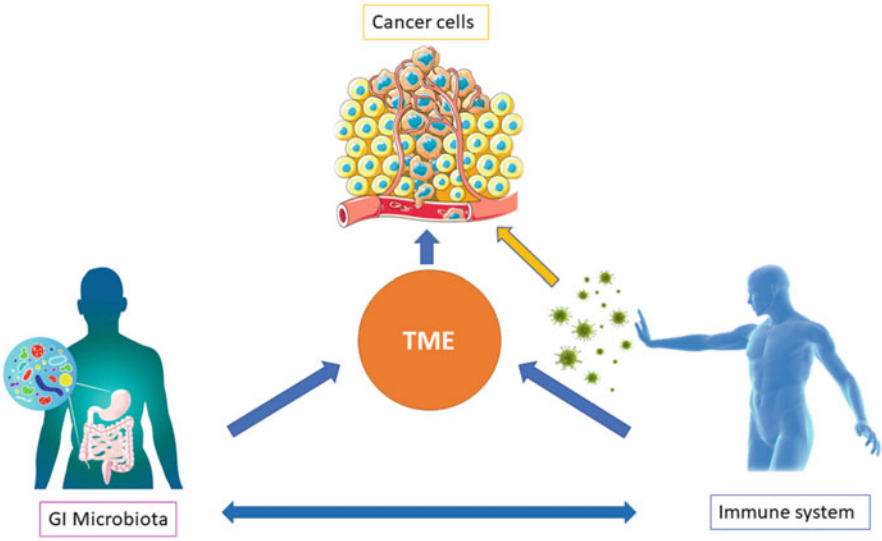

Fig. 1 The GI microbiota and immune system interact in a complex network with the cancer cells through a TME modulation. The GI microbiota can influence TME and thus tumor growth in both a positive or negative way and can also modulate the immune responses. Cancer growth is inhibited by the host immune system, which can be stimulated by the GI bacteria. Cancer can affect the host immunity by activating immunosuppressive pathways and can also modulate the GI flora

microbiota, changing its structure and functions during cancer development (Vivarelli et al. 2019). In healthy individuals, GI microflora acts as a symbiont, protecting against invading pathogens and avoiding cancer development (Pickard et al. 2017). When the fine equilibrium of this commensal bacterial community is destroyed, a dysbiosis state can develop, which can lead to pathological processes in the host, such as cancer (Cugini et al. 2021). Finally, increasing data on the TME physiology has suggested new targets within to improve cancer alternative therapies.

In this chapter, we would like to reconsider the TME state of the art to define its boards within the holobiont (defined as the assemblage of a host and the many other species living in or around it, which together form a discrete ecological unit) vision and to assess its interaction with microbiota and their reciprocal influence in GI cancers. We will discuss how disequilibria (dysbiosis) could influence the mutual relationship between the host immunity and intestinal bacteria affecting oncogenesis, tumor progression, and response to immunotherapy treatment.

2 The Borders of GIT Microenvironment

In the past, tumors have traditionally been considered genetic disorders, which means that the main approach in the field of oncology, especially after the innovations brought by the molecular turn in biomedicine, has been to identify the

biological (genetic) signature of the tumor. This approach has certainly paid off (both in terms of mechanistic comprehension and therapeutic intervention), but it has also clearly marked the understanding of cancer phenomena. In particular, the causes of GIT cancer have consequently been thought of as intrinsically linked to specific properties of tissues and cells in which it takes place.

However, starting from the development of a pluralistic perspective on the origins of GIT cancers, and tumors in general, among all we can first remember the famous work by Hanahan and Weinberg (2000, 2011) where greater attention has also been paid to context-dependent causes (think, for instance, of the epigenetic dimension). Furthermore, greater importance has been progressively given to the idea that cancer, like any biological phenomenon, is profoundly determined and shaped (both in its genesis and development) by the environment that surrounds it and therefore in its so-called ecological dimension. Conversely, in this systemic feature, the environment enclosing the tumor is also affected by it.

Therefore, in recent years, the TME concept has progressively been imposed in both research and clinical contexts. Despite its significance, a precise definition of microenvironment is still to come. This is due not only to the difficulty of experimentally characterizing the microenvironment but also for theoretical reasons. Indeed, from a purely molecular perspective, phenomena of an ecological nature (therefore interdependent with each other) present challenges both at an experimental and theoretical level. Specifically, such difficulties reverberate on the nature of the cause–effect relationship. In other words, it is particularly hard to dissect, in a purely mechanistic way, how much the microenvironment (prior to the tumor onset) guarantees the conditions for the development of the tumor itself and how much the intrinsic tumorigenic events lead to the formation of a specific microenvironment that is crucial for the disease development. Furthermore, one might wonder, spatially, how far the microenvironment extends, and whether distant but precise effects inherent to the onset of the disease (such as specific aspects of regulatory/organismal pathways) should be considered part of it or not (Laplane et al. 2018, 2019).

Considering these difficulties, which see both experimental and conceptual dimensions deeply intertwined, some scholars have recently proposed a sort of microenvironment taxonomy (Laplane et al. 2018). This specification, even according to the authors, should not be thought of as exhaustive or fixed but rather as an indication of the opportunity to have a more pluralistic approach and a greater description granularity of these phenomena.

According to this perspective, the authors distinguish at least six different levels (both in structural and functional terms) of the microenvironment: (1) *tumor cell to tumor cell environment* (TCTCE), that is, the one that develops from the specific interaction between tumor cells; (2) the *tumor niche* (CN) consisting of a more or less circumscribed portion of tissue that has certain characteristics (such as the relationship between tumor cells and the still healthy proximal context); (3) the *confined TME* (CTME) understood as that part of the microenvironment within the cancerous lesions; (4) the *proximal TEM* (PrTEM), i.e., the microenvironment adjacent to the tumor mass; (5) the *peripheral TEM* (PeTEM), i.e., those parts of the organism not strictly part of the tumor context but that are functionally connected

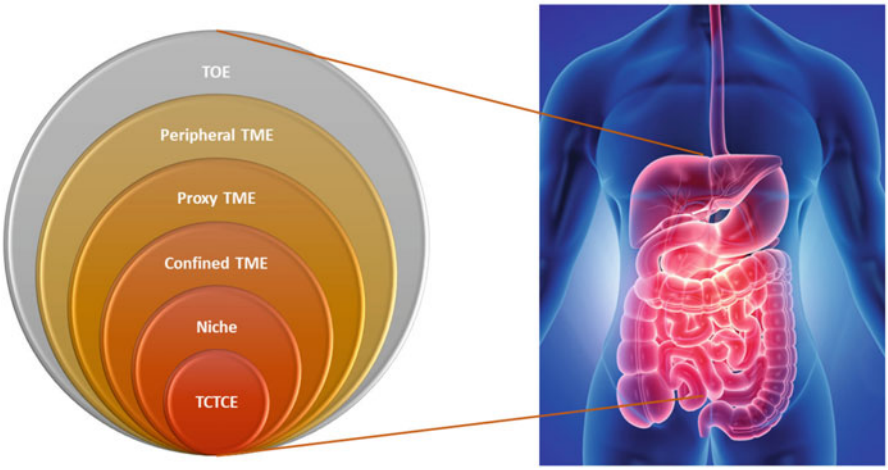

Fig. 2 The multiple layers of the tumor environment. The figure depicts the different TME layers (TCTCE, tumor–cell to tumor–cell environment; TOE, tumor organismal environment). (Adapted from Laplane et al. 2018)

to it (e.g., lymph nodes); and finally, (6) the *tumor organismal environment* (TOE), which refers to all those macrofunctions or regulatory regions that, although very distant from the tumor, can influence its genesis and development (Fig. 2).

Interestingly, whereas the purely molecular approach is used to consider biological phenomena in an isolated way, relatively to more or less circumscribed portions of biological substratum, the ecological view also allows us to make a point of a conceptual nature, remembering how something like a disease is not a fixed, static object that can be easily circumscribed in a single point but should rather be seen as a process that involves, to different degrees, diverse levels of interaction within the organism, if not the organism itself.

The perspective that extends to the organism as such the privilege of being at the center of both scientific research and therapeutic investigation should not be interpreted in a vague way. Indeed, this approach does not reject the advances and discoveries made by focusing on specific anatomical sites and distinctive mechanisms, but rather inserts them into a broader framework. On the one hand, this vision well represents the research developments increasingly aimed to integrate elements and processes previously ascribed only to single systems. An explicative example is the growth of studies focusing on the interconnections between the immune, endocrine, and nervous systems (both central and enteric) (Pérez et al. 2021).

On the other hand, even if only focusing on the immunological aspects, different scholars seem to suggest that it is the action field of a system such as the immune system is the organism as a whole (Poon and Farber 2020).

This perspective change shows how the notion of the microenvironment, also by virtue of its ecological nature, can and should be inserted into a frame that is more representative of the different levels of biological organization and their close interconnection and interdependence.

Thus, the disease study, especially in tumors, now presents challenges that force researchers and clinicians to consider it, in a unitary way, within its ecological scalability: from the distinctive molecular mechanisms to the global organismic response. Deprived of its context, even the microenvironment notion risks becoming too reductionist an instrument, both in terms of explanation and as a target of therapeutic activity. In other words, it is not possible to study and use the microenvironment in a profitable way if we want to consider it in a pure, purified, and isolated way rather than fully inserted in its systemic dimension.

This view change is even more necessary if we consider that the concept of the organism itself is also undergoing profound revision.

In particular, the so-called *holobiontic dimension* has become increasingly popular, according to which biological individuals macroscopically understood, such as animals and plants, are actually functional (not occasional) associations of different species (Boem et al. 2021; Bordenstein and Theis 2015).

A particularly important example is the kind of holobiontic integration between the human part (often called the "host") and its microbiota. Indeed, considering the tumors, more studies suggest that the microbiota not only contributes to specific local TME characteristics but, by virtue of its systematic nature and pervasiveness at the organismic level, it is capable of influencing numerous global functions and therefore directly and indirectly interacting with the disease development (Laplane et al. 2019; Wong-Rolle et al. 2021).

Microbiota's ability to modulate immune activities (both locally and at a general level) or to directly influence some pathways (both at the tissue and organismic level) (Chiu et al. 2017) makes it a privileged actor in the TME study both in its meaning of "context of proximity" to the tumor and also, in a broader perspective, including the entire biological individual.

3 The New "Actors" of the TME: The Gut Microbiota and Its Metabolites

3.1 The Microbiota of the Gastrointestinal Tract

Previously, the human body was thought to be a self-sustaining organism, able to control all the complexity of its cellular metabolism. However, different recent studies have demonstrated that the human body is, in fact, an ecosystem that included also trillions of microorganisms, which are known as "microbiota." The human microbiota could contain a number of microorganisms that is 10 times more than the total number of human cells in the body. The microbiota inhabits all the body surfaces exposed to the surrounding environment, such as mucosa tissues and the skin, from the GI to the respiratory and urogenital tracts.

This human GIT ecosystem is the outcome of an evolutionary process between microflora and the mammalian body. It encompasses the greatest amount of microbes able to generate compounds used as nutrients, thus creating a favorable setting for colonization; indeed, the colon includes more than 70% of all body microbial flora. It is important to highlight that the microbiota has a crucial effect on physiological mechanisms like food digestion and immune system reactions (Belkaid and Hand 2014).

Regarding its composition, it consists of microorganisms from the *Archaea*, *Bacteria*, *Eukarya*, and viruses. The majority of bacteria are strict anaerobes, with also facultative anaerobes and aerobes. Although commensal bacteria are symbiotic, they can cause pathology after translocation through the mucosa or in particular conditions, such as immunodeficiency (Maier et al. 2014).

Overall, the composition of the commensal bacteria is personal, but the richness of the bacterial population profile among body districts is greater than it is between individuals (Berg et al. 2020). A bacterial community that is commonly present in multiple body sites can be referred to as the "core" of a healthy microbiota (Rinninella et al. 2019).

Over 50 bacterial phyla have been defined but only 2 of them dominate the normal GIT flora: *Bacteroidetes* and *Firmicutes*, with *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Cyanobacteria* in marginal proportions (Jandhyala et al. 2015). The amount of microbial species living in the human intestine varies greatly between people, but, according to study on multiple subjects, the total human enteric microflora is composed of over 35,000 bacterial species (Thursby and Juge 2017). Approximately 70% of bacteria cannot be cultured using standard microbiological methods; indeed, traditional culture-based methods only detect about 30% of our microbiota (Ito et al. 2019). Nowadays, genomic next-generation sequencing (NGS) approach is critical for detecting the bacterial microbiota composition and metagenome, and these techniques provide more evidence about the relevance of the microbial community in host metabolic activities, cancer evolution, and inflammation.

The oral cavity, stomach, small intestine, and colon are the four distinct sites of the human GIT, each with its own activity as a specific microbial community. The enteric mucosa is the body's largest area that is persistently subjected to microbial and nutritional antigens. However, the organization of the intestinal flora is not uniform. Bacterial concentration in the human GIT increases from the mouth (less than 200 species) to the colon (bacteria reaching 1,010–1,012/g luminal content, with anaerobe bacteria predominating) (Sędzikowska and Szablewski 2021). In addition, the microbial structure shifts between these GIT locations. The comparison of biopsy samples of the small intestine with the colon from healthy controls showed that several microbial strains are increased at different sections. *Bacilli* of the *Firmicutes* and *Actinobacteria* are abundant in small intestine specimens. The intestinal epithelium is divided from the lumen by a dense mucus layer, resulting in significant latitudinal heterogeneity in microbiota communities. The microbiota of the gut lumen is greatly different from the microflora incorporated in the mucus layer, as well as the microbial community resident in the epithelium. Numerous

types of bacteria found in the intestinal lumen were unable to enter the mucus layer or epithelial crypts. *Streptococcus*, *Bacteroides*, *Bifidobacterium*, members of the *Enterobacteriaceae*, *Enterococcus*, *Clostridium*, *Lactobacillus*, and *Ruminococcus* were all found in feces, but only *Clostridium*, *Lactobacillus*, and *Enterococcus* were found in the small intestine's mucus layer and epithelial crypts (Dieterich et al. 2018).

Bacterial pathways (enzymes, metabolic activity, adhesion capacity), host elements (bile acids, mucus pH, digestive enzymes, transit time), and nonhost factors could all make a contribution to the modifications along the GIT length (medication, nutrients, environmental factors) (Rowland et al. 2018). The GI microflora is important to host metabolism because it generates compounds that interact with the host and implements important metabolic functions. The GM members, in particular, are a first defense against pathogen invasion and break down indigestible dietary components (Rowland et al. 2018), promote angiogenesis, support fat metabolism, synthesize vitamins, aid in immune system development, and maintain homeostasis (Kho and Lal 2018) (Fig. 3).

The microbial community is isolated from the internal gut milieu by a layer of epithelial cells that act as a barrier, balancing the crosstalk between the immune host system and the external environment. Moreover, epithelial layers are able to counteract microorganism invasion; indeed, adaptive and innate immune responses

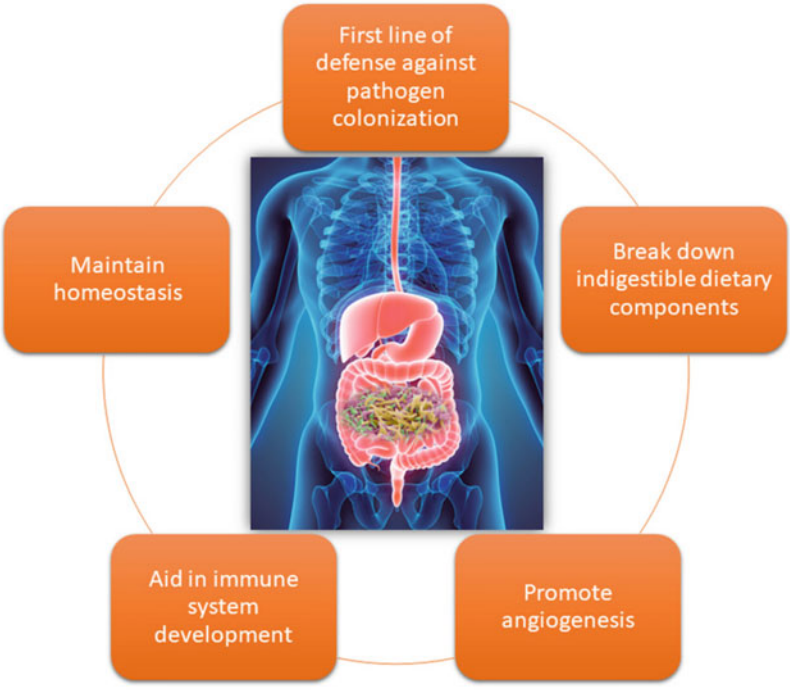

Fig. 3 The main functions of GI microbiota members

protect the mucosa and internal environment of the human body. Nearly 80% of immunological cells are involved in the mucosal-associated immune system, with the majority of these cells residing in the GIT, where the level of immunogenic food components and bacterial flora is highest in comparison to other areas of the body (Russo et al. 2016).

Normally, the microbial flora does not induce a pro-inflammatory response since the immune system recognizes the commensal bacteria and maintains homeostasis; however, when these pathways are compromised (e.g., use of antibiotics, immunodeficiency, and unhealthy diets) or new pathogenic bacteria are presented into this balanced system, the immune system reacts to the microbial population, activating a pathological condition and fostering inflammation and tumor growth in the GIT (Russo et al. 2016).

Several studies suggest that a disequilibrium of the intestinal flora and its metabolic activities is associated with the onset and development of GI pathologies such as colorectal cancer (CRC), functional dyspepsia, severe diarrhea, inflammatory bowel disease (IBD), celiac disease, and irritable bowel syndrome (IBS) (Nagao-Kitamoto et al. 2016; Yu et al. 2021). It is already comprehended that the GM imbalance (dysbiosis) can be triggered by both intrinsic (e.g., stress, genetics, and aging) and extrinsic factors (e.g., appendectomy, diet, and antibiotic use) (Padhi et al. 2022).

3.2 Alteration of Microbiota in the GI Cancers

The relationship between cancer, TME, and microbes is intricate and complex. GM may influence tumor development affecting the TME by inducing oxidative stress, genotoxicity, host immune response disturbance, and chronic inflammation. Alteration in microbiome composition, linked to oncogenesis and cancer progression, has been observed in several GIT compartments. Regarding the esophageal cancers, a general decreased species' abundance is detected in esophageal squamous cell carcinoma and esophageal adenocarcinoma (the two distinct histological types), as well as Barrett's esophagus (a precancerous lesion of the esophageal adenocarcinoma) compared with normal esophageal tissue. Genera that appeared enriched in Barrett's esophagus are *Streptococcus, Campylobacter, Prevotella,* and *Veillonella*. In esophageal squamous cell carcinoma, *Streptococcus* species, *Veillonella parvula*, and *Porphyromonas gingivalis* are the most abundant species, whereas *Lautropia*, *Peptococcus, Treponema, Corynebacterium, Moryella,* and *Cardiobacterium* genera are depleted (Liu et al. 2018; Smet et al. 2022).

Moreover, *Fusobacteria* is enriched in esophageal squamous cell carcinoma compared with controls (Shao et al. 2019). An enrichment of *Lactobacillus fermentum*, *Enterobacteriaceae*, *Prevotella, Leptotrichia,* and *Akkermansia muciniphila*, and a depletion of *Streptococci* have been observed in esophageal adenocarcinoma (Shao et al. 2019; Snider et al. 2019).

Furthermore, epidemiological data shows an opposite relation between *Helicobacter pylori* eradication and the occurrence of esophageal adenocarcinoma,

which could be caused by a change in the gastric microbial community (Peek Jr. and Blaser 2002). In addition, *H. pylori* infection has been indicated as one of the most frequent direct causes of gastric cancer (Yu et al. 2017). Indeed, recent evidence suggests that *H. pylori* may stimulate the local immune response (Amedei et al. 2003, 2014; Orsini et al. 2007) to gastric mucosa through generation of inflammatory molecules, such as chemokines and cytokines within gastric tissues, for further oncogenic changes caused by other microbes (Coker et al. 2018). However, a lot of research has demonstrated that stomach dysbiosis, involving multiple bacteria communities, is a dynamic phenomenon that correlates with cancer progression. So, for the progression and metastasis of gastric cancer, a synergistic interplay among the TME elements, such as *H. pylori* infection, immune cells and mediators, and different proteins, along with matrix metalloproteinases, is essential (Li and Yu 2020; Sohn et al. 2017). Moreover, CRC has been linked to microbial signature variations within the tumor differing from the bacterial assemblage of the adjacent normal tissue. These alterations include decreased diversity and perturbations in the community structure, which become more pronounced as the CRC progresses (Fang et al. 2021). Reduced amounts of favorable significant protective clades, such as butyrate-producing species from *Clostridium* clusters IV and XIV have been reported in CRC, whereas an increase in species such as *Fusobacterium*, *Campylobacter*, *Escherichia*, *Bacteroides*, and *Porphyromonas* has been attributed to an increase in pro-oncogenic capacity (Russo et al. 2017). In addition, *Fusobacterium nucleatum* frequently is found in CRC tissue, both at the adenoma and adenocarcinoma stages, grouped with other oral commensal species, including *Leptotrichia*, *Peptostreptococcus*, and *Campylobacter* species. Because of its ability to localize with tumor-enriched lectins via the outer membrane protein [fatty acid-binding protein 2 (Fap2)], *F. nucleatum* is commonly encountered at higher levels in the TME. Furthermore, *F. nucleatum* alters the TME by inhibiting the natural killer (NK) cells' antitumor responses and promoting the myeloid cell recruiting process. Bacterial profiles related to *Fusobacterium*-enriched but not *Fusobacterium*-negative malignancies were found in distant metastases, indicating that *F. nucleatum* affects also microbial metastatic dissemination (Russo et al. 2017). The microbiota members that have been associated with CRC tumorigenesis are enterotoxigenic *Bacteroides fragilis* (ETBF), *Escherichia coli*, *Streptococcus gallolyticus*, and *Enterococcus faecalis*.

Numerous studies have looked into the GM role in hepatocellular carcinoma (Bartolini et al. 2021). An increase in the richness of pro-inflammatory intestinal communities, such as *Proteobacteria* and *Enterobacteriaceae,* has been observed. Besides, some studies found that microbiome changes are linked to lower levels of butyrate-producing *Clostridiales* and anti-inflammatory species such as *A. muciniphila*. All these strains may affect the cancer's overall pro-inflammatory phenotype (Komiyama et al. 2021).

In recent years, evidence has shown that bacteria take part in the beginning and progression of cancer at sites previously considered sterile, such as pancreas (Nejman et al. 2020). In pancreatic cancer, bacteria belonging to the *Proteobacteria* phylum were the most represented (Nejman et al. 2020). Moreover, also alteration in

species belonging to the *Enterobacteriaceae* and *Pseudomonadaceae* families was observed (Geller et al. 2017). The most prevalent bacteria phyla in the pancreas TME included *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* (Li et al. 2021). In addition to intratumoral dysbiosis, other reports have shown a difference in the GM between pancreas of tumor patients and healthy controls, with increase in *Bacteroidetes* and lower *Firmicutes* (Ren et al. 2017). Finally, another study suggests that *Fusobacterium* species are linked to a worse prognosis in pancreatic cancer, meaning that they could be used as a predictive biomarker (Mitsuhashi et al. 2015).

3.3 Microbial Post-biotics of the GI Tract

Because the host–microbiome relationship in GI tumors has only recently been discovered, other mechanisms, such as aberrant cell-to-cell connections and the generation, conversion, and sensing in the TME of bacterial bioactive small molecules, known as "post-biotics," could be involved. Notably, post-biotics are "nonviable" bacterial products or metabolic by-products (metabolites) of probiotic microorganisms that promote biological activity in the host (Patel and Denning 2013).

Microbiome-modulated post-biotics (MMPBs) have the potential to affect host pathways such as proliferation, differentiation, migration, and cellular death. Furthermore, MMPBs may influence mucosal maturation and activity, as well as systemic immunity (Gaudet et al. 2015). The study of bacterial post-biotics as messengers between GM and immune system could in part clarify the deficient host–microbial interconnections within the TME in GI cancer. More understanding of how GM metabolic activity can influence the host immune system (immunomodulation) may strengthen translation to clinical applications.

However, GM communicates with the host through the generation of metabolites such as small chain fatty acids (SCFAs), tryptophan (Trp) catabolites, and bile acids. The MMPBs are engaged in differentiated bioactive activities for the host cells, resulting in a wide range of pathophysiological effects (Brestoff and Artis 2013).

SCFAs are the most investigated MMPBs in GI cancer, and their production is influenced by diet; indeed, they are secondary compounds generated through the fermentation of nutritional substrates, such as proteins, peptides, resistant starches, and undigested fibers by the GM. They represent a class of fatty acids with fewer than six carbons (such as acetic, formic, propionic, butyric, and valeric acid) whose generation is shaped by a number of factors, including host diets and GM variability with the presence of specific commensal bacteria (Canfora et al. 2015). The *Bacteroidetes* phylum mainly produces acetate and propionate, whereas the *Firmicutes* phylum secretes butyrate (Magne et al. 2020). SCFAs are a source of energy for local colonocytes within the eukaryotic TME, but they can be also transported to blood circulation and many other tissues. Intriguingly, the amount of the primary SCFAs (butyrate, acetate, and propionate) can vary across the entire digestive tract and can have different production ratios and physiological activities. Indeed, the synthesis of the various fermentation products varies depending on the

microbial community and environmental factors such as pH, hydrogen partial pressure, and available substrates. As for the SCFAs synthesis, acetate, which is the most represented SCFA, is generated by GM as a fermentation product, but also by acetogenic bacteria, from H_2 and CO_2. Propionate and acetate were found in both large and small intestines, with a larger ratio of butyrate in the cecum and colon (Vogt et al. 2015).

Propionate can be generated through the lactate pathway by *Firmicutes* and/or succinate pathway by *Bacteroidetes* phylum (Louis et al. 2014), while succinate is a metabolic end product for some bacteria, and specialist succinate utilizers convert most of the succinate into propionate (Macfarlane and Macfarlane 2003). Even so, while butyrate is a favorable source of energy for gut epithelial cells and has a low level in the systemic circulation, propionate is mostly metabolized in the liver, and only acetate has elevated concentrations in peripheral blood (Sleeth et al. 2010). SCFAs have also modulatory effects on immune system cells. Indeed, their role is to ensure the gut barrier's status quo and regulate the activation and proliferation of T-regulatory cells (Tregs), able to help the body maintain control during inflammation-induced T helper (Th) cell activity. As a result, a lack of SCFAs leads to a decrease in Tregs in the tissue, which indirectly favors the recruitment and proliferation of Th17 cells, thereby promoting inflammatory processes in the gut mucosa (Camilleri et al. 2019). The recent findings of SCFAs' ability to bind receptors such as GPR41, GPR43, and GPR109a (G-protein-coupled receptors that are typically expressed on a wide variety of cell types) allowed for the clarification of SCFA regulatory activity in GI cancer, suppressing inflammation and oncogenesis in the colon (Singh et al. 2014). Butyrate, and to a lesser extent propionate, has been found to affect CD8+ T cell signaling pathways, increasing the expression of IFN-γ and granzyme B. Butyrate stimulates histone deacetylation via HDAC inhibition, resulting in higher expression of CD8+ T cell effector molecules (Luu et al. 2018).

Furthermore, metabolomic analyses revealed an altered level of Trp and Trp metabolites in patients with GI disorders, in addition to altered SCFA levels (Wyatt and Greathouse 2021; Russo et al. 2019) Trp metabolic activity via the kynurenine (Kyn) pathway, as well as microbial modification of Trp to indolic complexes, is critical for host health and is both altered in cancer development. Changes in tryptophan metabolism begin early in CRC development as an adaptive mechanism for the tumor to evade immune surveillance and metastasize. Moreover, Trp metabolism by bacteria may involve multiple pathways as it is a substrate for both intestinal mucosa and bacterial enzymes (Nozaki and Ishimura 1972). Trp is produced from dietary substrates and is absorbed by SLC6A19/B0AT1 (a sodium-dependent neutral amino acid transporter) (Hashimoto et al. 2012). It is a precursor for many MMPBs and can perform a variety of host functions, including immune homeostasis and inflammatory response. The Trp availability is required for protein synthesis, production of indole and nicotinamide derivatives via kynurenine, and synthesis of serotonin (Richard et al. 2009).

Bile acids (BAs) are primarily synthesized in the liver and secreted to the gallbladder before being released into the duodenum, following food consumption. The amount and composition of the BA pool in the digestive tract can be modified by GM via primary to secondary BA biotransformation.

They are essential for maintaining a healthy GM, lipid and carbohydrate metabolism, insulin sensitivity, and innate immunity. The BA not only promotes emulsification and fat solubilization, but also increase the expression of a nuclear bile acid receptor (FXR) and a membrane G protein-coupled receptor (TGR5). This compound represents the mechanistic connections between BA and development of GI cancer. The reduction in secondary BA synthesis, caused by GM dysbiosis, reduces the activation of nuclear receptors FXR and TGR5 in the ileum, resulting in retained bile salts, increased gut permeability, small bowel translocation, and bacterial overgrowth, all of which make a significant contribution to hepatic diseases (Sinal et al. 2000). The FXR plays a major role in mediating intermodulation between the host and GM, specifically through regulation of enterohepatic BA circulation. FXR regulates BA levels via a tissue-specific mechanism (Goodwin et al. 2000). In addition, mouse models showed that FXR activation, stimulated by BA compounds (converted by GM), may preserve against bacterial overgrowth, gut permeability, and small bowel translocation (Inagaki et al. 2006). The degree of FXR activation may be modulated by GM dysbiosis, which causes BA variation and, as a result, liver disease caused by retained bile salts and a leaky gut. Bacteria translocated from the intestinal tract may also reduce FXR activation in hepatocytes, resulting in decreased BSEP (bile salt export pum) activity.

4 The Microbiota–Immunity Axis

4.1 The "Immune" TME

As previously reported, immune cells play a major role in the TME, in suppressing or promoting tumor growth, inducing a dynamic and ever-changing condition (Whiteside 2008). From the immunological point of view, the TME shows different composition depending on the type of tumor, but hallmark features include immune cells, such as T and B cells, macrophages, NK cells, neutrophils, dendritic cells (DCs), stromal cells, blood vessels, and extracellular matrix (Fig. 4).

A persistent inflammatory state is a common feature underlying the development of malignant neoplasm in several types of GI cancer, including CRC and hepatocellular (Patel 2020). Broadly, immune cells are represented by innate and adaptive cells. In particular, innate immunity is a nonspecific defense system that kicks in the hours after a foreign antigen enters the body, represented by macrophages, neutrophils, NK, and DCs. On the other hand, adaptive immunity is triggered by antigen exposure and uses an immunological memory to counteract a threat and improve immune responses. This type of immune defense includes T, B, and NK cells (Černý and Střížˇ 2019). In this regard, there are various specific populations of T cells that influence carcinogenesis within the TME. In detail, cytotoxic T cells ($CD8^+$) are the immune cells that detect abnormal tumor antigens expressed on cancer cells and are able to destroy them. However, the presence of cytotoxic T cells in the TME is frequently linked to a better prediction in cancer patients. In addition,

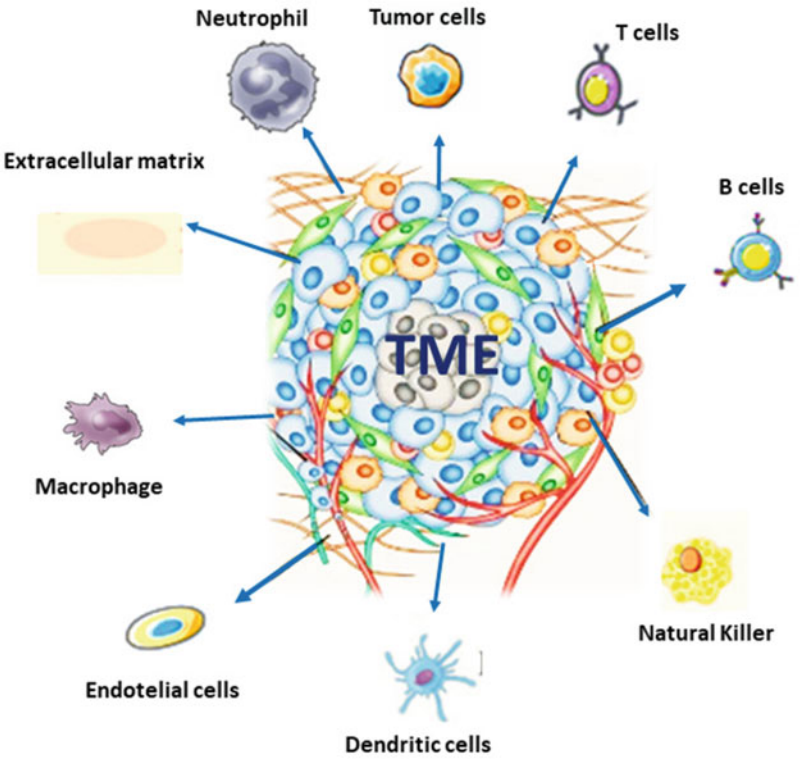

Fig. 4 Immune tumor microenvironment. The TME composition differs between cancer types. TME generally includes immune cells, such as T and B cells, NK cells, macrophages, neutrophils, DCs, endothelial cells, extracellular matrix, and tumor cells

in order to kill tumor cells, cytotoxic T cells inhibit angiogenesis by secreting IFN-γ (Manjarrez-Orduño et al. 2018). Within the TME framework, the $CD4^+$ T-cells differentiate into a number of subtypes and hence coordinate a wide range of immunological responses. Moreover, Th-1 cells are pro-inflammatory $CD4^+$ T cells that secrete interleukin-2 (IL-2) and IFN-γ to assist $CD8^+$ cells (van der Leun et al. 2020). Increased levels of Th-1 cells in the TME have been linked to better outcomes in a variety of cancers (Anderson and Simon 2020; Niccolai et al. 2017). In comparison to T cells, the TME owns a small number of invading B cells, known for producing antibodies' immune cells. They are able to present antigens and secrete cytokines. B cells are most commonly found in the tumor borders and in lymph nodes near the TME. Tumor-infiltrating B cells are required for the formation of "tertiary lymphoid structures," which are ectopic lymphoid structures within the TME. In addition, antitumorigenic activities of B cells include antigen presentation to T cells, production of antitumor antibodies, and secretion of cytokines promoting cytotoxic immune responses (Anderson and Simon 2020). On the other hand, the

presence of B cells in the TME can predict a poor prognosis in several cancers, such as bladder cancer. Finally, the regulatory B cells promote tumor growth by secreting cytokines (such as IL-10) that inhibit macrophage, neutrophil and cytotoxic T-cell immune responses (Černý and Stříž 2019; Li et al. 2020).

A recent study has revealed that NK cells are also regulatory cells that interact with DCs, macrophages, T cells, and endothelial cells in a reciprocal manner (Vivier et al. 2008). NK cells can be usually classified into two types, based on their function: those that directly participate in cell-mediated tumor cell death and those that release inflammatory cytokines. In general, NK cells are extremely effective at killing circulating tumor cells, but their cytotoxic action is less effective at killing tumor cells in TME. In most cancers, the infiltrated macrophages have been shown to have an important role in providing an immunosuppressive microenvironment for tumor growth. In fact, macrophages are a key component of the innate immune system that regulates immune responses by phagocytozing pathogens and presenting antigens. Two distinct subsets have been described: M1 and M2 macrophages (Martinez et al. 2009). Typically, M1 macrophages phagocytize and kill cells, and immune-suppressive M2 macrophages, which aid in wound healing. While both types of macrophages can be found within the tumor, the TME supports tumor growth and progression by promoting the M2 phenotype, through hypoxia and the production of some cytokines (e.g., IL-4). In several cancer types, such as gastric cancer, high macrophage infiltration is associated with a poor prognosis (Hao et al. 2012).

As one of the most abundant leukocytes in the immune system, neutrophils play a pivotal role in cancer progression via different processes, including angiogenesis, immunosuppression, and cancer metastasis (Wu et al. 2019). In fact, depending on the type of tumor and the disease stage, neutrophils can either prevent or enhance tumor growth. As a tumor grows, neutrophils are drawn to the TME, where they contribute to the inflammation increase by releasing cytokines and reactive oxygen species (ROS), which promote tumor cell death (Wu et al. 2020). Furthermore, tumor cells' aberrant metabolism produces metabolic alterations in TME (e.g., hyperglycolysis, lactate, and lipid deposition), which inhibit the activity of another antigen-presenting cell (APC) DCs (Peng et al. 2021). DCs help to initiate pathogen-specific T-cell responses by bridging the gap between adaptive and innate immunity. DCs' fate is determined by the TME, which can provide environmental signals that either cause an immune response to tumor cells or allow them to pass. DCs are triggered to tolerate the presence of tumor cells through cytokines released by the TME, which prevent the formation of an immune response (Du et al. 2018). Finally, cancer cells attract supporting cells from the adjacent endogenous stroma to promote critical phases of tumor formation. The stromal cell composition differs widely between tumor types and includes vessel endothelial cells, fibroblasts, adipocytes, and stellate cells. Once attracted to the TME, stromal cells release a range of factors that promote angiogenesis, proliferation, invasion, and metastasis (Denton et al. 2018).

4.2 The Role of Microbiota–Immunity Axis in Gastrointestinal Cancers

As result, for the aforementioned processes, GM and the host immune system have established a viable two-way relationship, ensuring the preservation of microbial eubiosis (Al-Rashidi 2022), described as the "microbiota–immunity axis" (Han et al. 2021; Jiao et al. 2020).

In particular, the highly active microbial population has been demonstrated to interact with the immune system of the host and play a variety of positive tasks, explaining also the host organism tolerance and the microbiota–immune balance (Romagnani 2006).

As previously mentioned, the dysbiosis condition could become a pivotal driver for various diseases, with distinct microbial profiles that can cause pathophysiology in several organs (Clemente et al. 2012; Lazar et al. 2018), including inflammation and cancer (Vivarelli et al. 2021). The presence of dysbiosis status induces dysregulated immune responses, so the host becomes more vulnerable to infections. Moreover, as immunotolerance is also affected, the immune system can react against the self-components with autoimmune reaction, which can vary in strength, being either overactivated (as in allergic reactions and chronic inflammation) or underactivated (as in immunodeficiency and malignancy) (Toor et al. 2019).

Regarding GI cancer, the microbiota immunity–axis influences tumor genesis and progression, both directly on tumor cells or indirectly, through the immune system modulation, affecting cancer immunosurveillance (Jain et al. 2021). In fact, a sophisticated interplay between host immune response, environmental variables, and microbial factors, such as *H. pylori* infection, can lead to gastric cancer (Nasr et al. 2020). As previously reported, colonization of the gastric mucosa by *H. pylori* induces a multiple immunity response that includes a local infiltration of immune cells, including neutrophils, macrophages, T and B cells, and cytokine secretion (Das et al. 2006). While this huge immune response occurs, *H. pylori* makes immune cell hyporeactive, suppressing their proliferation and production of interferon-gamma (IFN-γ) (Das et al. 2006). In this way, a downregulation of immune surveillance mechanisms occurs and the transformed cells evade the apoptosis mechanisms. Concerning CRC, the microbiota–immunity interaction appears to play a key role in all development stages, from oncogenesis to therapy and prognosis (Bartolini et al. 2020). This mechanism is expressed in particular through *F. nucleatum*, which promotes cancer through cell proliferation and immune response suppression (Nosho et al. 2016). *Fusobacterium* species can promote tumor growth by inducing multiple immunosuppressive adaptations, inhibiting immune response, and increasing myeloid-derived suppressor cells and tumor-associated macrophages inside colorectal tumors (Park et al. 2017). In particular, *F. nucleatum* has been implicated in a decrease in $CD3^+$ T lymphocytes, as well as in an increase in the production of cytokines with claimed pro-tumor effect, such as IL-6, IL-12, IL-17, and TNF-α, IL-12, and IL-17, and in a suppression of Th cell activity (Chen et al. 2017; Mima et al. 2016). Among all, IL-17 and IL-22, in particular, can be secreted even after a stimulation of Th17 cells induced by a

pro-inflammatory state caused by a dysbiotic microbiota (Russo et al. 2016; Wu et al. 2009). Similarly, some strains of *E. coli* and *B. fragilis* can induce a DNA damage by producing genotoxins, such as *B. fragilis* toxin and colibactin toxin, already found in patients with adenomatous polyposis (S. Wu et al. 2009). In detail, these toxins can induce an intestinal tissue damage, trigger chronic intestinal inflammation, and play a crucial role in the CRC development (Cheng et al. 2020). In pancreatic cancer, bacteria increase myeloid-derived suppressor cell recruitment, suppressing the Th1 immune response, and promoting IL-17 release. All these immunosuppressive consequences also contribute to immunotherapy lack of success (Huber et al. 2020). In addition, a recent study has found increased incidence of oral bacteria including *F. nucleatum* in cystic lesions of human pancreas (Gaiser et al. 2019). Similarly, a large amount of *F. nucleatum* was also found on bile samples from gallbladder cancer patients (Tsuchiya et al. 2018). To protect the host from infections and illnesses, the intestinal barrier, immune response, and microbiota interact in a dynamic process. A change in GM composition can activate the mucosal immune response, leading homeostasis to be disrupted. In this scenario, bacteria and immune cells migrate to the liver, causing inflammation-mediated liver damage and possibly paving the way for chronic hepatic disease and liver cancer (Bartolini et al. 2021; Peterson and Artis 2014; Yang et al. 2020).

The liver immune system is characterized by cells of the innate immune system, including Kupffer cells, NK cells, and a particular abundance of cells from the adaptive immunity, especially T cells (both αβ and γδ). The role of γδT cells in liver cancer is controversial and depends mainly on subsets and disease stage. In fact, on the one hand, their ability to infiltrate tumors causing the progression of liver cancer and, on the other hand, their cytotoxic action combined with NK cells seem to be able to prevent the recurrence of hepatocellular carcinoma (Zhou et al. 2020). Related to this, microbiota plays an important role in maintaining the homeostasis of hepatic γδT cells. In detail, the mechanism could be attributed to lipid antigens, a microbiota component, which activates hepatic γδT cells and produces IL-17A. Hence, the activated γδT17 cells act on their pro-inflammatory and anti-infection abilities, exasperating liver cancer (Xi et al. 2019). In addition, increased intestinal permeability during liver cancer allows bacterial translocation into the liver, particularly *Lactobacillus gasseri*. As a result, liver T cells secrete IL-17A in response to microbial stimulation, aggravating liver disease (Tedesco et al. 2018).

In conclusion, a thorough knowledge of the microbiota–immune axis will provide light on the fundamental mechanisms behind GM dysbiosis and its impact on liver diseases, including cancer.

Hence, microbiota–immune axis can also predict disease progression and survival, as well as influence how well cancer treatment works. The ability to manipulate the microbiota can be used to improve the efficacy of immunotherapies while lowering their toxicity (Yi et al. 2019). In particular, increasing data suggests that gut dysbiosis may have a direct impact on local and systemic antitumor immunity. In addition, recurrent antibiotic exposure, which impairs intestine eubiosis and promotes the spread of gut infections, has been linked to an increased cancer risk (Cianci et al. 2019). In general, dysbiosis may play a role in tumor formation or the failure of immune checkpoint inhibitor-based therapy (Shui et al. 2019).

5 Targeting TME for Cancer Immunotherapies

Numerous studies have documented the potential for using microbiota – and its derived immune metabolism – within the TME as a new therapeutic target for cancer (Suraya et al. 2020). Because GM influences both innate and adaptive cancer immunity, it is interesting to presume that it may contribute to regulating antitumor immunity induced by chemotherapy, radiotherapy, and immunotherapy.

Regarding immunotherapy, today the ability to stimulate antitumor T cell responses that block inhibitory T cell signaling pathways has transformed the treatment for cancer. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that identify specific membrane receptors on the surface of T cells, preventing tumor cells from inhibiting them. The programmed cell death protein 1 (PD-1) and its ligand are the targets of the most widely used monoclonal antibodies' ICIs (Pardoll 2015). Immunotherapy has significantly improved the overall survival of cancer patients. Nevertheless, only a small percentage of patients benefit from ICIs (Jiang and Zhou 2015), and the explanations for this phenomenon are not entirely known (Russo et al. 2020). It is important to note that the latest study emphasizes the function of microbiota within TME in defining immune responses to ICI treatment (Sears and Pardoll 2018), characterizing tumor-infiltrating lymphocytes (TILs). In addition, TILs appear to be involved in response to checkpoint inhibition (Cesano and Warren 2018).

Mouse models are used to observe the relation between ICIs and particular microbiota members (Sivan et al. 2015) (Vetizou et al. 2015; Taur et al. 2014), suggesting that the efficacy of checkpoint blockade could be improved through microbiota modulation (Fig. 5). Moreover, melanoma growth in mice was different on the basis of distinct microbiota profile. Variations in antitumor immune-mediated response, particularly in intratumoral $CD8^+$ T cell accumulation and tumor-specific T-cell responses, were documented. Intriguingly, upon cohousing or after fecal microbial flora transplantation (FMT), it was observed that the different antitumor immune-mediated response was reset (Sivan et al. 2015).

Bacteroides and *Burkholderia* were linked to the GM antitumor activity in another study that looked at subjects with various malignancy, including antibiotic treatment during a CTLA-4 (protein receptor that functions as an immune checkpoint) treatment. In response to these bacteria, innate immune cells produce IL-12, which can activate the adaptive immune response, stimulating T cells (Vetizou et al. 2015). Furthermore, a rise in *Collinsella aerofaciens*, *Enterococcus faecium*, and *Bifidobacterium longum* was found through the GM evaluation of patients who responded positively to PD-1 blockade. When fecal specimens from responders patients were transferred to germ-free mice, tumor growth was moderate and therapeutic activity was better than in mice that received samples from nonresponder patients. Additionally, an increase in CD8+ T cells and reduced Tregs were observed in the TME (Matson et al. 2018). These exploratory mouse investigations supported the crucial GM involvement in cancer ICI treatment and incentivized clinical investigation to establish the impact of the microflora on ICI therapies. Moreover, another study showed that primary resistance to ICIs can be related to abnormal

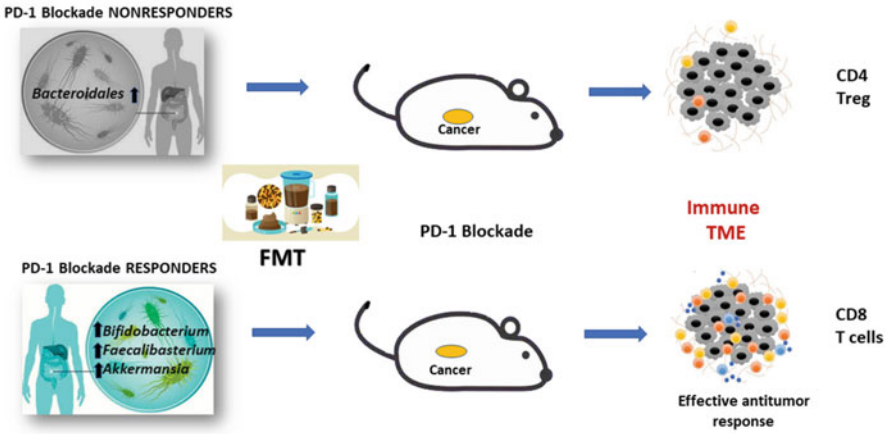

Fig. 5 Gut microbiota impact on the efficacy of PD-1 blockade. Specific GM profiles correlate with response to PD-1 blockade in tumor patients. Fecal microbiota transplantation (FMT) from responders into mice improves responses to anti-PD-1 treatment and is correlated with increased anticancer $CD8^+$ cells in the tumor environment. Mice receiving FMT from nonresponders' patients did not benefit from anti-PD-1 therapy, and tumor microenvironment is enriched in immune-suppressive $CD4^+$ Tregs

enteric microbiota profiles, demonstrating that anti-PD-1/PD-L1 treatment was effective in patients with advanced epithelial malignancy who were not treated with antibiotics, particularly in comparison to the results of those who did receive antibiotics (Routy et al. 2018). This finding suggests that antibiotic therapy can damage GM, damaging immune checkpoint blockade response. In addition, patients responding to PD-1 blockade showed a distinctive microbial structure, enriched in *Akkermansia* and *Alistipes*. Furthermore, germ-free mice were treated with FMT using fecal samples from responding patients prior to anti-PD-1 therapy. The immune response was reported to be increased in these mice while the immune response of germ-free mice treated with FMT from nonresponders was recovered by oral supplementation with *A. muciniphila*. By increasing the enrolment of CXCR3 + CCR9+ CD4+ T cells into mouse tumor beds, these bacteria improved the efficacy of PD-1 blockade in an IL-12-dependent process (Routy et al. 2018).

Gopalakrishnan and colleagues studied the oral flora and GM of patients with metastatic melanoma receiving anti-PD-1 therapy. Regarding the systemic immune responses, gut samples enriched in *Clostridiales*, *Ruminococcaceae*, or *Faecalibacterium* from patients with malignancy showed more effector T cells (CD4+ and CD8+) in the peripheral blood and a protected cytokine response to anti-PD-1 treatment. On the other hand, patients whose gut samples were enriched in *Bacteroidales* had higher frequencies of Tregs and a reduced cytokine response to anti-PD-1 treatment (Gopalakrishnan et al. 2018). Immune profiling revealed increased antitumor and systemic immunity in melanoma patients responding to therapies showing a favorable enteric microbial flora, as well as in germ-free mice receiving FMT from responding subjects.

However, GM can also cause toxicity to immune checkpoint blockade. This consequence was first detected in animal models and then in patients (Chaput et al. 2017), (Frankel et al. 2017), (Zitvogel et al. 2017). The microbial taxa related to this effect belong to *Firmicutes* phylum and *Ruminococcaceae* family (Gopalakrishnan et al. 2018), (Chaput et al. 2017), (Frankel et al. 2017). In contrast, microbiota taxa that do not respond to ICIs belong to *Bacteroidales* order; however, an abundance in these taxa generally reduces the ratio of toxicity (Gopalakrishnan et al. 2018), (Chaput et al. 2017), (Frankel et al. 2017).

6 Conclusion

The multifaceted series of events that lead to the evolution and progression of GI cancer, as well as its intense interaction with the surrounding TME, should be investigated further, especially in light of the presence of the microbiota–immunity axis, which certainly contributes to enlarging the TME boundaries.

Cancer treatment has undergone a revolution in the last decade (Russo et al. 2020). Previously, drugs targeted tumors more broadly (e.g., chemotherapy), but novel therapeutic approaches target particular cells within the TME. While therapeutically targeting the TME is an appealing strategy for cancer treatment, existing FDA-approved treatments are ineffective. As we learn more about how the TME contributes to tumorigenesis, new therapeutic targets and strategies will emerge.

In this scenario, understanding the multiple layers of tumor microenvironment, as well as the reciprocal interactions among its members, can help to implement better therapeutic regimes for cancer management; however, a more integrated and pluralistic approach using combination of strategies appears to be more effective than single modalities because tumor heterogeneity arises from a variety of signaling pathways/crosstalks that exist in the network of communicating cancer cells.

Compliance with Ethical Standards The authors declare that there is no conflict of interest.

References

Al-Rashidi HE (2022) Gut microbiota and immunity relevance in eubiosis and dysbiosis. Saudi J Biol Sci 29(3):1628–1643. https://doi.org/10.1016/j.sjbs.2021.10.068

Amedei A, Bergman MP, Appelmelk BJ, Azzurri A, Benagiano M, Tamburini C et al (2003) Molecular mimicry between Helicobacter pylori antigens and H+, K+ − adenosine triphosphatase in human gastric autoimmunity. J Exp Med 198(8):1147–1156. https://doi.org/10.1084/jem.20030530

Amedei A, Munari F, Bella CD, Niccolai E, Benagiano M, Bencini L et al (2014) Helicobacter pylori secreted peptidyl prolyl cis, trans-isomerase drives Th17 inflammation in gastric adenocarcinoma. Intern Emerg Med 9(3):303–309. https://doi.org/10.1007/s11739-012-0867-9

Anderson NM, Simon MC (2020) The tumor microenvironment. Curr Biol 30(16):R921–r925. https://doi.org/10.1016/j.cub.2020.06.081

Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F (2020) Global burden of 5 major types of gastrointestinal cancer. Gastroenterology *159*(1):335–349.e315. https://doi.org/10.1053/j.gastro.2020.02.068

Bartolini I, Risaliti M, Ringressi MN, Melli F, Nannini G, Amedei A et al (2020) Role of gut microbiota-immunity axis in patients undergoing surgery for colorectal cancer: focus on short and long-term outcomes. World J Gastroenterol 26(20):2498–2513. https://doi.org/10.3748/wjg.v26.i20.2498

Bartolini I, Risaliti M, Tucci R, Muiesan P, Ringressi MN, Taddei A, Amedei A (2021) Gut microbiota and immune system in liver cancer: promising therapeutic implication from development to treatment. World J Gastrointest Oncol 13(11):1616–1631. https://doi.org/10.4251/wjgo.v13.i11.1616

Belkaid Y, Hand TW (2014) Role of the microbiota in immunity and inflammation. Cell 157(1):121–141. https://doi.org/10.1016/j.cell.2014.03.011

Berg G, Rybakova D, Fischer D, Cernava T, Vergès MC, Charles T et al (2020) Microbiome definition re-visited: old concepts and new challenges. Microbiome 8(1):103. https://doi.org/10.1186/s40168-020-00875-0

Boem F, Ferretti G, Zipoli Caiani S (2021) Out of our skull, in our skin: the microbiota-gut-brain axis and the extended cognition thesis. Biol Philos 36(2):14. https://doi.org/10.1007/s10539-021-09790-6

Bordenstein SR, Theis KR (2015) Host biology in light of the microbiome: ten principles of Holobionts and Hologenomes. PLoS Biol 13(8):e1002226. https://doi.org/10.1371/journal.pbio.1002226

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492

Brestoff JR, Artis D (2013) Commensal bacteria at the interface of host metabolism and the immune system. Nat Immunol 14(7):676–684. https://doi.org/10.1038/ni.2640

Camilleri M, Lyle BJ, Madsen KL, Sonnenburg J, Verbeke K, Wu GD (2019) Role for diet in normal gut barrier function: developing guidance within the framework of food-labeling regulations. Am J Physiol Gastrointest Liver Physiol 317(1):G17–g39. https://doi.org/10.1152/ajpgi.00063.2019

Canfora EE, Jocken JW, Blaak EE (2015) Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol 11(10):577–591. https://doi.org/10.1038/nrendo.2015.128

Černý J, Stříž I (2019) Adaptive innate immunity or innate adaptive immunity? Clin Sci (Lond) 133(14):1549–1565. https://doi.org/10.1042/cs20180548

Cesano A, Warren S (2018) Bringing the next generation of immuno-oncology biomarkers to the clinic. Biomedicine 6(1). https://doi.org/10.3390/biomedicines6010014

Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C et al (2017) Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 28(6):1368–1379. https://doi.org/10.1093/annonc/mdx108

Chen J, Pitmon E, Wang K (2017) Microbiome, inflammation and colorectal cancer. Semin Immunol 32:43–53. https://doi.org/10.1016/j.smim.2017.09.006

Cheng WT, Kantilal HK, Davamani F (2020) The mechanism of Bacteroides fragilis toxin contributes to colon cancer formation. Malays J Med Sci *27*(4):9–21. https://doi.org/10.21315/mjms2020.27.4.2

Chiu L, Bazin T, Truchetet ME, Schaeverbeke T, Delhaes L, Pradeu T (2017) Protective microbiota: from localized to long-reaching co-immunity. Front Immunol 8:1678. https://doi.org/10.3389/fimmu.2017.01678

Cianci R, Franza L, Schinzari G, Rossi E, Ianiro G, Tortora G et al (2019) The interplay between immunity and microbiota at intestinal immunological niche: the case of cancer. Int J Mol Sci 20(3). https://doi.org/10.3390/ijms20030501

Clemente JC, Ursell LK, Parfrey LW, Knight R (2012) The impact of the gut microbiota on human health: an integrative view. Cell 148(6):1258–1270. https://doi.org/10.1016/j.cell.2012.01.035
Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G et al (2018) Mucosal microbiome dysbiosis in gastric carcinogenesis. Gut 67(6):1024–1032. https://doi.org/10.1136/gutjnl-2017-314281
Cugini C, Ramasubbu N, Tsiagbe VK, Fine DH (2021) Dysbiosis from a microbial and host perspective relative to oral health and disease. Front Microbiol 12:617485. https://doi.org/10.3389/fmicb.2021.617485
Das S, Suarez G, Beswick EJ, Sierra JC, Graham DY, Reyes VE (2006) Expression of B7-H1 on gastric epithelial cells: its potential role in regulating T cells during helicobacter pylori infection. J Immunol 176(5):3000–3009. https://doi.org/10.4049/jimmunol.176.5.3000
Denton AE, Roberts EW, Fearon DT (2018) Stromal cells in the tumor microenvironment. Adv Exp Med Biol 1060:99–114. https://doi.org/10.1007/978-3-319-78127-3_6
Dieterich W, Schink M, Zopf Y (2018) Microbiota in the gastrointestinal tract. Med Sci (Basel) 6(4). https://doi.org/10.3390/medsci6040116
Du X, Chapman NM, Chi H (2018) Emerging roles of cellular metabolism in regulating dendritic cell subsets and function. Front Cell Dev Biol 6:152. https://doi.org/10.3389/fcell.2018.00152
Fang CY, Chen JS, Hsu BM, Hussain B, Rathod J, Lee KH (2021) Colorectal cancer stage-specific fecal bacterial community fingerprinting of the Taiwanese population and underpinning of potential taxonomic biomarkers. Microorganisms 9(8). https://doi.org/10.3390/microorganisms9081548
Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, Koh AY (2017) Metagenomic shotgun sequencing and unbiased Metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia 19(10):848–855. https://doi.org/10.1016/j.neo.2017.08.004
Gaiser RA, Halimi A, Alkharaan H, Lu L, Davanian H, Healy K et al (2019) Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer. Gut 68(12):2186–2194. https://doi.org/10.1136/gutjnl-2018-317458
Gaudet RG, Sintsova A, Buckwalter CM, Leung N, Cochrane A, Li J et al (2015) INNATE IMMUNITY. Cytosolic detection of the bacterial metabolite HBP activates TIFA-dependent innate immunity. Science 348(6240):1251–1255. https://doi.org/10.1126/science.aaa4921
Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D et al (2017) Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science 357(6356):1156–1160. https://doi.org/10.1126/science.aah5043
Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB et al (2000) A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell 6(3):517–526. https://doi.org/10.1016/s1097-2765(00)00051-4
Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV et al (2018) Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359(6371):97–103. https://doi.org/10.1126/science.aan4236
Han P, Gu JQ, Li LS, Wang XY, Wang HT, Wang Y et al (2021) The association between intestinal bacteria and allergic diseases-cause or consequence? Front Cell Infect Microbiol 11:650893. https://doi.org/10.3389/fcimb.2021.650893
Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70. https://doi.org/10.1016/s0092-8674(00)81683-9
Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674. https://doi.org/10.1016/j.cell.2011.02.013
Hao NB, Lü MH, Fan YH, Cao YL, Zhang ZR, Yang SM (2012) Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol 2012:948098. https://doi.org/10.1155/2012/948098
Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M et al (2012) ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 487(7408):477–481. https://doi.org/10.1038/nature11228

Huber M, Brehm CU, Gress TM, Buchholz M, Alashkar Alhamwe B, von Strandmann EP et al (2020) The immune microenvironment in pancreatic cancer. Int J Mol Sci 21(19). https://doi.org/10.3390/ijms21197307

Inagaki T, Moschetta A, Lee YK, Peng L, Zhao G, Downes M et al (2006) Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. Proc Natl Acad Sci U S A 103(10):3920–3925. https://doi.org/10.1073/pnas.0509592103

Ito T, Sekizuka T, Kishi N, Yamashita A, Kuroda M (2019) Conventional culture methods with commercially available media unveil the presence of novel culturable bacteria. Gut Microbes 10(1):77–91. https://doi.org/10.1080/19490976.2018.1491265

Jain T, Sharma P, Are AC, Vickers SM, Dudeja V (2021) New insights into the cancer-microbiome-immune Axis: decrypting a decade of discoveries. Front Immunol 12:622064. https://doi.org/10.3389/fimmu.2021.622064

Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D (2015) Role of the normal gut microbiota. World J Gastroenterol 21(29):8787–8803. https://doi.org/10.3748/wjg.v21.i29.8787

Jiang T, Zhou C (2015) The past, present and future of immunotherapy against tumor. Transl Lung Cancer Res 4(3):253–264. https://doi.org/10.3978/j.issn.2218-6751.2015.01.06

Jiao Y, Wu L, Huntington ND, Zhang X (2020) Crosstalk between gut microbiota and innate immunity and its implication in autoimmune diseases. Front Immunol 11:282. https://doi.org/10.3389/fimmu.2020.00282

Kho ZY, Lal SK (2018) The human gut microbiome - a potential controller of wellness and disease. Front Microbiol 9:1835. https://doi.org/10.3389/fmicb.2018.01835

Komiyama S, Yamada T, Takemura N, Kokudo N, Hase K, Kawamura YI (2021) Profiling of tumour-associated microbiota in human hepatocellular carcinoma. Sci Rep 11(1):10589. https://doi.org/10.1038/s41598-021-89963-1

Laplane L, Duluc D, Larmonier N, Pradeu T, Bikfalvi A (2018) The multiple layers of the tumor environment. Trends Cancer 4(12):802–809. https://doi.org/10.1016/j.trecan.2018.10.002

Laplane L, Duluc D, Bikfalvi A, Larmonier N, Pradeu T (2019) Beyond the tumour microenvironment. Int J Cancer 145(10):2611–2618. https://doi.org/10.1002/ijc.32343

Lazar V, Ditu LM, Pircalabioru GG, Gheorghe I, Curutiu C, Holban AM et al (2018) Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Front Immunol 9:1830. https://doi.org/10.3389/fimmu.2018.01830

Li Q, Yu H (2020) The role of non-H. pylori bacteria in the development of gastric cancer. Am J Cancer Res 10(8):2271–2281

Li C, Jiang P, Wei S, Xu X, Wang J (2020) Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. Mol Cancer 19(1):116. https://doi.org/10.1186/s12943-020-01234-1

Li JJ, Zhu M, Kashyap PC, Chia N, Tran NH, McWilliams RR et al (2021) The role of microbiome in pancreatic cancer. Cancer Metastasis Rev 40(3):777–789. https://doi.org/10.1007/s10555-021-09982-2

Liu Y, Lin Z, Lin Y, Chen Y, Peng XE, He F et al (2018) Streptococcus and Prevotella are associated with the prognosis of oesophageal squamous cell carcinoma. J Med Microbiol 67(8):1058–1068. https://doi.org/10.1099/jmm.0.000754

Louis P, Hold GL, Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12(10):661–672. https://doi.org/10.1038/nrmicro3344

Luu M, Weigand K, Wedi F, Breidenbend C, Leister H, Pautz S et al (2018) Regulation of the effector function of CD8+ T cells by gut microbiota-derived metabolite butyrate. Sci Rep 8(1):14430. https://doi.org/10.1038/s41598-018-32860-x

Macfarlane S, Macfarlane GT (2003) Bacterial growth on mucosal surfaces and biofilms in the large bowel. In: Devine D, Wilson M (eds) Medical implications of biofilms. Cambridge University Press, Cambridge, pp 262–286

Magne F, Gotteland M, Gauthier L, Zazueta A, Pesoa S, Navarrete P, Balamurugan R (2020) The Firmicutes/Bacteroidetes ratio: a relevant marker of gut Dysbiosis in obese patients? Nutrients 12(5). https://doi.org/10.3390/nu12051474

Maier E, Anderson RC, Roy NC (2014) Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. Nutrients 7(1):45–73. https://doi.org/10.3390/nu7010045

Manjarrez-Orduño N, Menard LC, Kansal S, Fischer P, Kakrecha B, Jiang C et al (2018) Circulating T cell subpopulations correlate with immune responses at the tumor site and clinical response to PD1 inhibition in non-small cell lung cancer. Front Immunol 9:1613. https://doi.org/10.3389/fimmu.2018.01613

Martinez FO, Helming L, Gordon S (2009) Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol 27:451–483. https://doi.org/10.1146/annurev.immunol.021908.132532

Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML et al (2018) The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359(6371):104–108. https://doi.org/10.1126/science.aao3290

Mima K, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA et al (2016) Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. Gut 65(12):1973–1980. https://doi.org/10.1136/gutjnl-2015-310101

Mitsuhashi K, Nosho K, Sukawa Y, Matsunaga Y, Ito M, Kurihara H et al (2015) Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis. Oncotarget *6*(9):7209–7220. https://doi.org/10.18632/oncotarget.3109

Nagao-Kitamoto H, Kitamoto S, Kuffa P, Kamada N (2016) Pathogenic role of the gut microbiota in gastrointestinal diseases. Intest Res 14(2):127–138. https://doi.org/10.5217/ir.2016.14.2.127

Nasr R, Shamseddine A, Mukherji D, Nassar F, Temraz S (2020) The crosstalk between microbiome and immune response in gastric cancer. Int J Mol Sci 21(18). https://doi.org/10.3390/ijms21186586

Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT et al (2020) The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science 368(6494):973–980. https://doi.org/10.1126/science.aay9189

Niccolai E, Ricci F, Russo E, Nannini G, Emmi G, Taddei A et al (2017) The different functional distribution of "not effector" T cells (Treg/Tnull) in colorectal cancer. Front Immunol 8:1900. https://doi.org/10.3389/fimmu.2017.01900

Nosho K, Sukawa Y, Adachi Y, Ito M, Mitsuhashi K, Kurihara H et al (2016) Association of Fusobacterium nucleatum with immunity and molecular alterations in colorectal cancer. World J Gastroenterol 22(2):557–566. https://doi.org/10.3748/wjg.v22.i2.557

Nozaki M, Ishimura Y (1972) Tryptophan metabolism in micro-organisms. Biochem J 128(1):24p–25p. https://doi.org/10.1042/bj1280024pc

Orsini B, Vivas JR, Ottanelli B, Amedei A, Surrenti E, Galli A et al (2007) Human gastric epithelium produces IL-4 and IL-4delta2 isoform only upon Helicobacter pylori infection. Int J Immunopathol Pharmacol 20(4):809–818. https://doi.org/10.1177/039463200702000417

Padhi P, Worth C, Zenitsky G, Jin H, Sambamurti K, Anantharam V et al (2022) Mechanistic insights into gut microbiome Dysbiosis-mediated Neuroimmune dysregulation and protein Misfolding and clearance in the pathogenesis of chronic neurodegenerative disorders. Front Neurosci 16:836605. https://doi.org/10.3389/fnins.2022.836605

Pardoll D (2015) Cancer and the immune system: basic concepts and targets for intervention. Semin Oncol 42(4):523–538. https://doi.org/10.1053/j.seminoncol.2015.05.003

Park HE, Kim JH, Cho NY, Lee HS, Kang GH (2017) Intratumoral fusobacterium nucleatum abundance correlates with macrophage infiltration and CDKN2A methylation in microsatellite-unstable colorectal carcinoma. Virchows Arch 471(3):329–336. https://doi.org/10.1007/s00428-017-2171-6

Patel A (2020) Benign vs Malignant tumors. JAMA Oncol 6(9):1488. https://doi.org/10.1001/jamaoncol.2020.2592

Patel RM, Denning PW (2013) Therapeutic use of prebiotics, probiotics, and postbiotics to prevent necrotizing enterocolitis: what is the current evidence? Clin Perinatol 40(1):11–25. https://doi.org/10.1016/j.clp.2012.12.002

Peek RM Jr, Blaser MJ (2002) Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat 939 Rev Cancer 2(1):28–37. https://doi.org/10.1038/nrc703

Peng X, He Y, Huang J, Tao Y, Liu S (2021) Metabolism of dendritic cells in tumor microenvironment: for immunotherapy. Front Immunol 12:613492. https://doi.org/10.3389/fimmu.2021.613492

Pérez AR, Maya-Monteiro CM, Carvalho VF (2021) Editorial: neuroendocrine-immunological interactions in health and disease. Front Endocrinol (Lausanne) 12:718893. https://doi.org/10.3389/fendo.2021.718893

Peterson LW, Artis D (2014) Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat Rev Immunol 14(3):141–153. https://doi.org/10.1038/nri3608

Pickard JM, Zeng MY, Caruso R, Núñez G (2017) Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev 279(1):70–89. https://doi.org/10.1111/imr.12567

Poon MML, Farber DL (2020) The whole body as the system in systems immunology. iScience 23(9):101509. https://doi.org/10.1016/j.isci.2020.101509

Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM (2014) Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 74(11):2913–2921. https://doi.org/10.1158/0008-5472.Can-14-0155

Ren Z, Jiang J, Xie H, Li A, Lu H, Xu S et al (2017) Gut microbial profile analysis by MiSeq sequencing of pancreatic carcinoma patients in China. Oncotarget *8*(56):95176–95191. https://doi.org/10.18632/oncotarget.18820

Richard DM, Dawes MA, Mathias CW, Acheson A, Hill-Kapturczak N, Dougherty DM (2009) L-tryptophan: basic metabolic functions, behavioral research and therapeutic indications. Int J Tryptophan Res 2:45–60. https://doi.org/10.4137/ijtr.s2129

Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC (2019) What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms 7(1). https://doi.org/10.3390/microorganisms7010014

Romagnani S (2006) Immunological tolerance and autoimmunity. Intern Emerg Med 1(3):187–196. https://doi.org/10.1007/bf02934736

Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R et al (2018) Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359(6371):91–97. https://doi.org/10.1126/science.aan3706

Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K (2018) Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr 57(1):1–24. https://doi.org/10.1007/s00394-017-1445-8

Russo E, Taddei A, Ringressi MN, Ricci F, Amedei A (2016) The interplay between the microbiome and the adaptive immune response in cancer development. Ther Adv Gastroenterol 9(4):594–605. https://doi.org/10.1177/1756283x16635082

Russo E, Bacci G, Chiellini C, Fagorzi C, Niccolai E, Taddei A et al (2017) Preliminary comparison of oral and intestinal human microbiota in patients with colorectal cancer: a pilot study. Front Microbiol 8:2699. https://doi.org/10.3389/fmicb.2017.02699

Russo E, Giudici F, Fiorindi C, Ficari F, Scaringi S, Amedei A (2019) Immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Front Immunol 10:2754. https://doi.org/10.3389/fimmu.2019.02754

Russo E, Nannini G, Dinu M, Pagliai G, Sofi F, Amedei A (2020) Exploring the food-gut axis in immunotherapy response of cancer patients. World J Gastroenterol 26(33):4919–4932. https://doi.org/10.3748/wjg.v26.i33.4919

Sears CL, Pardoll DM (2018) The intestinal microbiome influences checkpoint blockade. Nat Med 24(3):254–255. https://doi.org/10.1038/nm.4511

Sędzikowska A, Szablewski L (2021) Human gut microbiota in health and selected cancers. Int J Mol Sci 22(24). https://doi.org/10.3390/ijms222413440

Shao D, Vogtmann E, Liu A, Qin J, Chen W, Abnet CC, Wei W (2019) Microbial characterization of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma from a high-risk region of China. Cancer 125(22):3993–4002. https://doi.org/10.1002/cncr.32403

Shui L, Yang X, Li J, Yi C, Sun Q, Zhu H (2019) Gut microbiome as a potential factor for modulating resistance to cancer immunotherapy. Front Immunol 10:2989. https://doi.org/10.3389/fimmu.2019.02989

Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, Gonzalez FJ (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. Cell 102(6):731–744. https://doi.org/10.1016/s0092-8674(00)00062-3

Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H et al (2014) Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity 40(1):128–139. https://doi.org/10.1016/j.immuni.2013.12.007

Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM et al (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350(6264):1084–1089. https://doi.org/10.1126/science.aac4255

Sleeth ML, Thompson EL, Ford HE, Zac-Varghese SE, Frost G (2010) Free fatty acid receptor 2 and nutrient sensing: a proposed role for fibre, fermentable carbohydrates and short-chain fatty acids in appetite regulation. Nutr Res Rev 23(1):135–145. https://doi.org/10.1017/s0954422410000089

Smet A, Kupcinskas J, Link A, Hold GL, Bornschein J (2022) The role of microbiota in gastrointestinal cancer and cancer treatment: chance or curse? Cell Mol Gastroenterol Hepatol 13(3):857–874. https://doi.org/10.1016/j.jcmgh.2021.08.013

Snider EJ, Compres G, Freedberg DE, Khiabanian H, Nobel YR, Stump S et al (2019) Alterations to the esophageal microbiome associated with progression from Barrett's esophagus to esophageal adenocarcinoma. Cancer Epidemiol Biomark Prev 28(10):1687–1693. https://doi.org/10.1158/1055-9965.Epi-19-0008

Sohn SH, Kim N, Jo HJ, Kim J, Park JH, Nam RH et al (2017) Analysis of gastric body microbiota by pyrosequencing: possible role of bacteria other than Helicobacter pylori in the gastric carcinogenesis. J Cancer Prev 22(2):115–125. https://doi.org/10.15430/jcp.2017.22.2.115

Suraya R, Nagano T, Kobayashi K, Nishimura Y (2020) Microbiome as a target for cancer therapy. Integr Cancer Ther 19:1534735420920721. https://doi.org/10.1177/1534735420920721

Taur Y, Jenq RR, Perales MA, Littmann ER, Morjaria S, Ling L et al (2014) The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 124(7):1174–1182. https://doi.org/10.1182/blood-2014-02-554725

Tedesco D, Thapa M, Chin CY, Ge Y, Gong M, Li J et al (2018) Alterations in intestinal microbiota Lead to production of interleukin 17 by intrahepatic γδ T-cell receptor-positive cells and pathogenesis of Cholestatic Liver Disease. Gastroenterology 154(8):2178–2193. https://doi.org/10.1053/j.gastro.2018.02.019

Thursby E, Juge N (2017) Introduction to the human gut microbiota. Biochem J 474(11):1823–1836. https://doi.org/10.1042/bcj20160510

Toor D, Wsson MK, Kumar P, Karthikeyan G, Kaushik NK, Goel C et al (2019) Dysbiosis disrupts gut immune homeostasis and promotes gastric diseases. Int J Mol Sci 20(10). https://doi.org/10.3390/ijms20102432

Tsuchiya Y, Loza E, Villa-Gomez G, Trujillo CC, Baez S, Asai T et al (2018) Metagenomics of microbial communities in gallbladder bile from patients with gallbladder cancer or Cholelithiasis. Asian Pac J Cancer Prev 19(4):961–967. https://doi.org/10.22034/apjcp.2018.19.4.961

van der Leun AM, Thommen DS, Schumacher TN (2020) CD8(+) T cell states in human cancer: insights from single-cell analysis. Nat Rev Cancer 20(4):218–232. https://doi.org/10.1038/s41568-019-0235-4

Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C et al (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350(6264): 1079–1084. https://doi.org/10.1126/science.aad1329

Vivarelli S, Falzone L, Leonardi GC, Salmeri M, Libra M (2021) Novel insights on gut microbiota manipulation and immune checkpoint inhibition in cancer (review). Int J Oncol 59(3). https://doi.org/10.3892/ijo.2021.5255

Vivarelli S, Salemi R, Candido S, Falzone L, Santagati M, Stefani S et al (2019) Gut microbiota and cancer: from pathogenesis to therapy. Cancers (Basel) 11(1). https://doi.org/10.3390/cancers11010038

Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S (2008) Functions of natural killer cells. Nat Immunol 9(5):503–510. https://doi.org/10.1038/ni1582

Vogt SL, Peña-Díaz J, Finlay BB (2015) Chemical communication in the gut: effects of microbiota-generated metabolites on gastrointestinal bacterial pathogens. Anaerobe 34:106–115. https://doi.org/10.1016/j.anaerobe.2015.05.002

Whiteside TL (2008) The tumor microenvironment and its role in promoting tumor growth. Oncogene 27(45):5904–5912. https://doi.org/10.1038/onc.2008.271

Wong-Rolle A, Wei HK, Zhao C, Jin C (2021) Unexpected guests in the tumor microenvironment: microbiome in cancer. Protein Cell 12(5):426–435. https://doi.org/10.1007/s13238-020-00813-8

Wu L, Saxena S, Awaji M, Singh RK (2019) Tumor-associated neutrophils in cancer: going pro. Cancers (Basel) 11(4). https://doi.org/10.3390/cancers11040564

Wu L, Saxena S, Singh RK (2020) Neutrophils in the tumor microenvironment. Adv Exp Med Biol 1224:1–20. https://doi.org/10.1007/978-3-030-35723-8_1

Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR et al (2009) A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 15(9):1016–1022. https://doi.org/10.1038/nm.2015

Wyatt M, Greathouse KL (2021) Targeting dietary and microbial tryptophan-indole metabolism as therapeutic approaches to colon cancer. Nutrients 13(4). https://doi.org/10.3390/nu13041189

Xi C, Jia Z, Xiaoli W, Na Z, He W, Hao J (2019) New aspect of liver IL-17(+)γδ T cells. Mol Immunol 107:41–43. https://doi.org/10.1016/j.molimm.2018.12.030

Yang X, Lu D, Zhuo J, Lin Z, Yang M, Xu X (2020) The gut-liver Axis in immune remodeling: new insight into liver diseases. Int J Biol Sci 16(13):2357–2366. https://doi.org/10.7150/ijbs.46405

Yi M, Jiao D, Qin S, Chu Q, Li A, Wu K (2019) Manipulating gut microbiota composition to enhance the therapeutic effect of cancer immunotherapy. Integr Cancer Ther 18: 1534735419876351. https://doi.org/10.1177/1534735419876351

Yu D, Meng X, de Vos WM, Wu H, Fang X, Maiti AK (2021) Implications of gut microbiota in complex human diseases. Int J Mol Sci 22(23). https://doi.org/10.3390/ijms222312661

Yu G, Torres J, Hu N, Medrano-Guzman R, Herrera-Goepfert R, Humphrys MS et al (2017) Molecular characterization of the human stomach microbiota in gastric cancer patients. Front Cell Infect Microbiol 7:302. https://doi.org/10.3389/fcimb.2017.00302

Zhou QH, Wu FT, Pang LT, Zhang TB, Chen Z (2020) Role of γδT cells in liver diseases and its relationship with intestinal microbiota. World J Gastroenterol 26(20):2559–2569. https://doi.org/10.3748/wjg.v26.i20.2559

Zitvogel L, Daillere R, Roberti MP, Routy B, Kroemer G (2017) Anticancer effects of the microbiome and its products. Nat Rev Microbiol 15(8):465–478. https://doi.org/10.1038/nrmicro.2017.44