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Impact of microbiota-immunity axis in pancreatic cancer management

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Abstract

The microbiota impact on human diseases is well-known, and a growing body of literature is providing evidence about the complex interplay between microbiota-immune system-human physiology/pathology, including cancers. Together with the defined risk factors (*e.g.*, smoke habits, diet, diabetes, and obesity), the oral, gut, biliary, and intrapancreatic microbiota contribute to pancreatic cancer development through different pathways including the interaction with the immune system. Unfortunately, a great majority of the pancreatic cancer patients received a diagnosis in advanced stages not amenable to be radically treated and potentially cured. Given the poor pancreatic cancer prognosis, complete knowledge of these complicated relationships could help researchers better understand the disease pathogenesis and thus provide early potential non-invasive biomarkers, new therapeutic targets, and tools for risk stratification that might result in greater therapeutic possibilities and eventually in a better and longer patient survival.

Key Words: Gastrointestinal tumors; Hepatopancreatobiliary tumors; Pancreatic cancer; Gut microbiota; Dysbiosis; Cancer development; Carcinogenesis

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Core Tip: Despite improvements in traditional patient treatment, pancreatic cancer remains a tumor with an increasing incidence and a poor prognosis, often diagnosed in late stages. The oral, gut, biliary, and intrapancreatic microbiota might contribute to pancreatic cancer through different pathways including a complex interplay with the immune system. Comprehending these complicated relationships could help researchers better understand the pathogenesis of pancreatic cancer, thus providing new promising options for early diagnosis, therapeutic targets, and risk stratification hoping that could translate into better and longer patient survival.

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INTRODUCTION

Pancreatic cancer (PanCa), with its most common subtype ductal adenocarcinoma, is a relatively uncommon but highly lethal neoplasm. Despite years of research, the PanCa patients are often diagnosed in advanced stages having less than a 30% chance of being alive 1 year after diagnosis and less than a 10% 5-year survival rate[1-3].

The human body is colonized by a huge number of microorganisms, which include bacteria, archaea, viruses, and fungi. This articulate community with the environment and the microorganism metabolites is known as microbiota. Usually, the commensal community lives in equilibrium with the host in a condition defined as "eubiosis;" however, if for some reason the equilibrium is broken, a condition called dysbiosis occurs[4]. A growing body of the literature reported the complex interplay of the microbiota with the immune system and the intestinal barrier in a bidirectional influence that plays a key role in health and disease, including cancer[5-7].

Evidence about the potential causal role of microbiota on PanCa development is still scarce, but it is gaining great attention over the last few years[8,9]. The oral, gut, biliary, and intrapancreatic microbiota seem to contribute to PanCa initiation and development. Furthermore, microbiota both act through a direct effect or indirectly through the interaction with the immune system or through the production of circulating toxins. Understanding these complicated relationships could help researchers better define the causes of different pathologies, including PanCa, and thus provide new therapeutic targets and tools for risk stratification[10].

Finally, given the diagnosis frequently made in advanced stages and the poor prognosis of this tumor together with the lack of markers able to detect an early PanCa, the chance to use the gut microbiota as an early non-invasive biomarker might result in greater therapeutic possibilities and, eventually, in a better and longer patient survival[11].

This review aims to provide the current state of the microbiota immunity axis impact in every step of PanCa, trying to highlight potential promising new therapeutic options.

CANCER DEVELOPMENT

Although often no identifiable risk factors can be found, genetic factors, lifestyle, and chronic pancreatitis are well-recognized[12]. It is notable that most of them cause dysbiosis too[1,12].

Because an estimated 70% of the bacteria in the human body have not been grown yet, studying the human microbiota is a difficult endeavor[13]. A breakthrough in DNA sequencing occurred in the mid-2000s thanks to next-generation sequencing[14]. Through gene sequencing, metagenomics, metatranscriptomics, metaproteomics, and metabolomics (the recently introduced "meta-omics" techniques) analysis of strain composition, production of metabolites, and other bacterial activities can be performed [15,16]. Consequently, the significant microbiota impact on human physiology and pathology has been increasingly acknowledged over the years. Although the evidence is still in its infancy, being a small part of more complex mechanisms, the potential role of the microbiome itself and microbiome-immune system interplay on PanCa onset and development has been recently advocated.

Different microbial compositions in healthy people and disease

Although whether changes in the balance between microbial species could be a cause or an effect of disease onset and development is difficult to state[17], microbial composition analyses have been performed in different districts including the oral cavity, duodenum, gut, bile, and pancreatic tissue. Conflicting results can be found in analyzing the studies, but the influence of other risk factors (for

example, smoking habit) may create bias and at least, partially explain some differences.

Association between periodontal disease or oral dysbiosis and several kinds of cancers (oral, hematological, digestive tract, prostate, uterus, lung, and breast) has been reported with different strengths of association[18]. In analyzing this relationship, PanCa has been one of the most studied cancers[16,18]. *Porphyromonas gingivalis*, *Fusobacterium*, and *Aggregatibacter actinomycetemcomitans* in the oral microbiota were related to a higher risk of developing PanCa[17,19,20]. Similarly, analyzing the saliva, the presence of *Streptococcus* and *Leptotrichia* was associated with a higher risk of human PanCa, and *Granulicatella adiacens* was found to be increased in these patients. On the contrary, the presence of *Veillonella* and *Neisseria* was associated with a lower risk of PanCa, and *Streptococcus mitis* appeared to be reduced in these patients[21-23]. Higher representation of *Prevotella* and *Vaillonella* was more frequently found in patients with jaundice[22].

Fusobacterium, *Rothia*, *Actinomyces*, *Corynebacterium*, *Atopobium*, *Peptostreptococcus*, *Catonella*, *Oribacterium*, *Filifactor*, *Campylobacter*, *Moraxella*, and *Tannerella* were more abundant in the PanCa patients' tongue coatings, while *Haemophilus*, *Porphyromonas*, and *Paraprevotella* were more abundant in healthy people. *Haemophilus* and *Porphyromonas* or *Leptotrichia* and *Fusobacterium* represented unique signatures able to identify healthy people or patients with PanCa[24].

Helicobacter pylori (*H. pylori*) is a well-known pathogenetic agent in gastric cancer, and its role in colorectal cancer development has also been suggested[25]. Being more represented in the stomach and duodenum of the PanCa patients than in controls, *H. pylori* could also have a role in the development of this cancer. It elicits chronic mucosal inflammation and alters the gut microbiota causing bacterial translocation[3,26]. However, this relationship is particularly argued due to the frequent associations with several other known risk factors thus precluding definitive conclusions[9].

Association between gut dysbiosis and several kinds of cancers (breast, lung, digestive tract, and above all colorectal) has been reported. Lower gut microbial biodiversity was found in stool samples of PanCa patients[27]. Furthermore, significantly higher levels of mucus-degrader Verrucomicrobia and Bacteroidetes including the Gram-negative bacteria lipopolysaccharide (LPS) producers *Prevotella* and *Hallella* together with other LPS producers *Veillonella*, *Klebsiella*, *Selenomonas*, and *Enterobacter* have been found in the gut microbiota of PanCa patients compared to healthy people. In parallel, lower levels of other Firmicutes, notably the butyrate-producers *Coprococcus* and *Anaerostipes*, have been found[2,27,28]. However, the exact clinical correlation is still unknown, and further studies are needed. Finally, higher levels of *Bifidobacterium pseudolongum* were documented in both gut and tumor specimens[28].

The pancreas is considered a sterile organ because of its alkaline pH and the presence of digestive enzymes that make bacterial proliferation difficult[29]. However, some potential ways through which microbes could reach it have been recently proposed even if definitive conclusions cannot be drawn. They include colonization from the duodenum or the biliary tract following reflux and colonization through the lymphatic and/or portal system[28]. Finally, the potential tissue contamination during sample collection and processing is another way of colonization. The majority of the human PanCa tissues were found to be colonized, mainly by *Gammaproteobacteria*[30-33], and a greater abundance of bacteria and fungi have been found in PanCa tissue of both human and animal models[28,30,31].

Acinetobacter, *Enterobacter*, *Pseudomonas*, *Delftia*, *Enterococcus*, *Streptococcus*, *Corynebacterium*, *Propionibacterium*, *Sphingomonas*, and *Staphylococcus* with a significant *Klebsiella* predominance were found in the human PanCa group compared to the healthy control (samples from organ donations)[32]. In addition, higher levels of *Malassezia* species in cancer tissue were related to PanCa progression, while *Candida*, *Aspergillus*, or *Saccharomyces* species did not cause cancer development after repopulation following mycobiome ablation[34]. In animal models, a relatively higher abundance of *Lactobacillus* was found in the pancreatic tissue of the control group, while a relatively higher abundance of *Fusobacterium* species and Proteobacteria were found in the pancreatic tissue of the cancer group[17,33]. Furthermore, significant differences have been discovered in microbiota composition found in different PanCa stages [28].

Finally, bile contamination, mainly related to biliary stenting and endoscopic procedures, was significantly found in patients affected by PanCa. The more represented species in bile samples (collected during endoscopic procedures or surgery) were *Escherichia coli* (*E. coli*) and different species of *Pseudomonas*, *Enterobacter*, and *Enterococcus*[34-37].

The main microbiota modifications are summarized in [Table 1](#).

Pathogenetic PanCa models

The pathogenetic relationship between microbiota and PanCa is far from being completely understood, and the proposed potential pathogenetic mechanisms are derived mainly from animal models[17]. The microbiota promotes carcinogenesis in direct or indirect ways. Indirect action could be elicited through the production of circulating toxins or harmful metabolites or through the interaction with the immune system. Both innate and adaptive immune responses are active in fighting human cancers[38]. The anti-cancer immunological mechanisms include the cytotoxic CD 8+ T cells, T helper (Th) cells, mature dendritic cells, macrophages, and natural killer cells. Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells able to suppress both innate and adaptive immunity with different mechanisms, promoting regulatory T cell development and simultaneously inhibiting the effector T cells and natural killer cells[39].

Table 1 Different microbial compositions in patients affected by pancreatic cancer

Anatomical district	Microbiota	Implications
Oral	Higher microbial biodiversity	Confer higher risk of developing PanCa[17,19,20,23]
	<i>Porphyromonas gingivalis</i> , <i>Fusobacterium</i>	
	<i>Aggregatibacter actinomycetemcomitans</i>	
	<i>Streptococcus</i> , <i>Leptotrichia</i> , <i>Neisseria elongata</i>	
	<i>Granulicatella adiacens</i>	More abundant in PanCa than control[23]
	<i>Fusobacterium</i> , <i>Rothia</i> , <i>Actinomyces</i>	
	<i>Corynebacterium</i> , <i>Atopobium</i>	
	<i>Peptostreptococcus</i> , <i>Catonella</i>	
	<i>Oribacterium</i> , <i>Filifactor</i>	
	<i>Campylobacter</i> , <i>Moraxella</i> , <i>Tannerella</i>	
	Fungi:	
<i>Candida</i>		
Gut	Bacteroidetes	More abundant in PanCa than control[27,28]
	<i>Prevotella</i> , <i>Hallella</i>	
	Proteobacteria	
	<i>Klebsiella</i> , <i>Enterobacter</i>	
	Verrucomicrobia	
	<i>Bifidobacterium pseudolongum</i>	
	<i>Veillonella</i>	
	Firmicutes	Less abundant in PanCa than control[27]
	<i>Coprococcus</i> , <i>Anaerostipes</i>	
Pancreas	Proteobacteria	More abundant in PanCa than control[17,28,30-33]
	Gamma proteobacteria	
	<i>Pseudomonas</i> , <i>Acinetobacter</i> , <i>Enterobacter</i>	
	<i>Delftia</i> , <i>Klebsiella</i> , <i>Sphingomonas</i>	
	Firmicutes	
	<i>Enterococcus</i> , <i>Streptococcus</i> , <i>Staphylococcus</i>	
	Fusobacteria	
	<i>Fusobacterium</i> species	
	Acinetobacteria	
	<i>Bifidobacterium pseudolongum</i>	
	<i>Corynebacterium</i> , <i>Propionibacterium</i>	
	<i>Lactobacillus</i>	Less abundant in PanCa than control[17,33]
	Fungi	Confer higher risk of PanCa progression[31]
	<i>Malassezia</i>	

PanCa: Pancreatic cancer.

Most of these models have also been reported in other cancer types.

A direct carcinogenic effect of *Porphyromonas gingivalis* is related to the apoptosis inhibition of the epithelial cells, the activation of the *p53* gene, and the induction of *KRAS* mutation, the latter two through the production of the enzyme peptidyl-arginine deiminase[40]. *KRAS* mutation can be found in almost all PanCa. Interestingly, germ-free *KRAS*-mutated mice demonstrated slower PanCa progression suggesting that gene mutation itself is not sufficient to cause cancer development[28,29]. Intestinal microbiota has a direct long-distance effect on PanCa development through up/downregulation of pro/anti-cancer pathways[32]. *Pseudomonas aeruginosa* is related to higher levels of the anti-apoptotic and pro-proliferative proteins Bel-XL, Mcl-1, survivin, c-Myc, and cyclin D1[41]. The hepatotropic viruses that cause hepatitis B or C can contribute to PanCa development through the modulation of the PI3K/AKT signaling pathway and tissue inflammation[22].

One of the most common bacterial components related to cancer development is LPS, which is a direct cause of *KRAS* gene mutation and can stimulate nuclear factor- κ B that further increases *KRAS* mutation risk. Furthermore, LPS is an activator of the toll-like receptor (TLR) signaling pathway thus enhancing pancreatic inflammation[21,29]. *H. pylori* is an LPS producer[29]. Deoxycholic acid, a bacterial metabolite of cholic acid, promotes carcinogenesis through the activation of the epidermal growth factor and STAT3 signaling pathway[2]. *Desulfovibrio vulgaris* and other sulfate-reducing bacteria produce genotoxic hydrogen sulfide when the diet is enriched in proteins and fats[42]. Other carcinogenic bacterial metabolites from proteolytic fermentation include phenols, ammonia, and other nitrogen-rich products. *Candida* induces PanCa through the production of the carcinogen nitrosamines or acetaldehyde[10,43].

Finally, many studies highlighted the role of the immune system on PanCa[44-46]. The activation of the immune system by the microbiota of different districts can cause local and/or systemic inflammation that worsen dysbiosis sustaining a vicious circle. For example, *H. pylori* presence in the stomach is related to reduced production of acid/achlorhydria that might trigger dysbiosis[9]. Gut dysbiosis induces chronic pancreatic inflammation. Pancreatic microbiota can further elicit an inflammatory response interacting with both innate and specific immune systems. The immunosuppressive cells, regulatory T cells and MDSC, are predominant at the expense of cytotoxic T lymphocytes, indicating that the phenotype is immunosuppressive[32,44,47]. This aspect implies that the immune system is faulty, most likely due to cancer itself, which causes local and systemic immunological dysfunction escaping the immune system's detection[48,49].

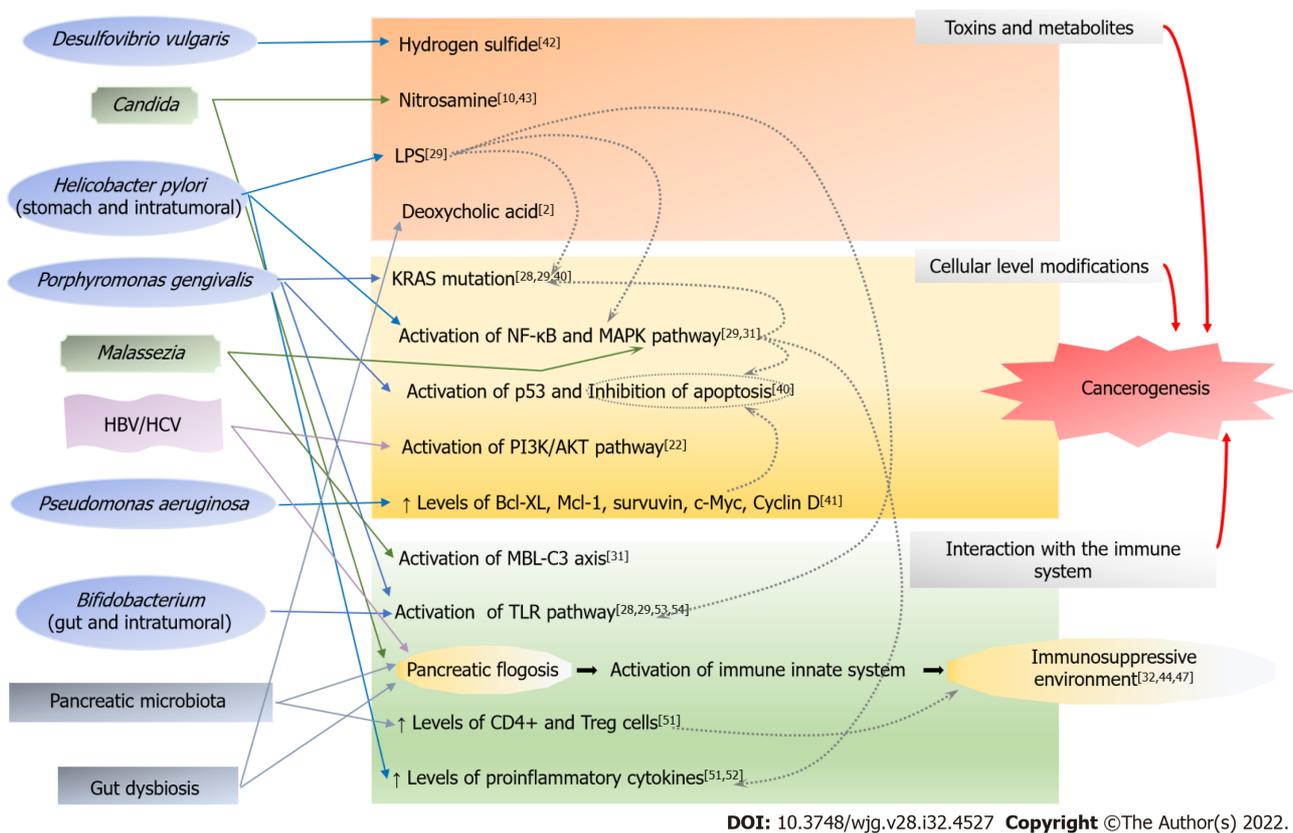
Furthermore, the tumor microenvironment contributes to the development of PanCa promoting a Th2 polarization with the production of higher levels of interleukin (IL)-17 and IL-10 and reduced production of interferon- γ , which promotes cancer progression[28,50]. The presence of this microenvironment kind and a dense stroma represents a unique PanCa peculiarity[51]. Interestingly, smoke habits impact microbiota inducing immunosuppression with reduced levels of IgG and the making of biofilms, hence possibly promoting the proliferation of harmful bacteria[30]. In an experimental setting, Pushalkar *et al*[28] demonstrated that germ-free mice did not show PanCa progression, while fecal microbiota transplantation received from sick mice hampered Th1 differentiation of CD4+ and activation of CD8+ T cells hence causing cancer progression.

In humans, *Citrobacter freundii* was found to be associated with immunosuppression and the activation of several oncogenic pathways. Furthermore, the enrichment of nine microbes including *Acidovorax ebreus* and *Shigella sonnei* was related to the downregulation of tumor-suppressive pathways and immune dysregulation with reduced levels of M2 macrophages, activated memory, and CD8+ T cells[51]. *H. pylori* infection of human PanCa tissue was reported to be associated with higher levels of IL-8 and vascular endothelial growth factor and with the proliferation of several factors including nuclear factor- κ B, activator protein 1, and serum response element[52].

Malassezia can interact with the MAPK pathway causing the production of high levels of proinflammatory cytokines, including IL-6, and can activate mast cells[31]. Similarly, *Trichosporon* can increase the level of IL-6, tumor necrosis factor- α , and interferon- γ [8]. *Candida* triggers inflammatory response (Th17-mediated), activating the MDSCs[10,43]. *Porphyromonas gingivalis* and *Aggregatibacter* activate, similarly to *Bifidobacterium pseudolongum*[53], the TLR signaling pathway increasing the risk of PanCa development in both animal models and humans[28,54]. Different studies documented that mice deficient in pattern recognition receptors signaling, including TLR 4, TLR7, TLR9, and mincle, show less PanCa progression[53,55,56].

In this scenario, another critical pattern recognition receptors is the mannose-binding lectin (MBL). The complement cascade is triggered when MBL binds to the glycans of the fungal wall, for example, *Malassezia*. The MBL-C3 axis might be involved in cancer development given that extratumoral suppression of MBL or C3 was associated with a lower risk of PanCa onset and MBL- or C3-deficient mice showed greater defense against PanCa progression[31].

Each component of the microbiota might be implicated in PanCa through different pathogenetic mechanisms and the role of fungal dysbiosis is still far from being completely explored and understood. **Figure 1** summarizes this complex relationship.



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Figure 1 Pathogenetic models. This figure aims at simplifying the complex interplay between microbiota in different anatomical districts and the immune system in carcinogenesis. Each component of the microbiota might be implicated in pancreatic cancer through different pathogenetic mechanisms. LPS: Lipopolysaccharide; NF-κB: Nuclear Factor κB; HBV/HCV: Hepatitis B/C virus; MBL: Mannose-binding lectin; TLR: Toll-like receptor; Treg: T regulatory.

CURRENT TREATMENTS FOR PanCa

Impact of microbiota in surgical treatment

Whenever technically feasible and oncologically appropriate, surgical treatment is the best chance of cure that could be offered to the patients.

In a small prospective study, both pre- and postoperative gut microbiota was found to be enriched in *Akkermansia*, *Aeromonas*, *Enterobacteriaceae*, *Bacteroidales* and decreased in *Lachnospiraceae*, *Prevotella*, and *Faecalitalea*. Furthermore, *Bacteroides* were more frequently associated with higher postoperative morbidity, longer hospital stays, and longer intensive care unit stay[57].

When patients present with severe jaundice, a biliary drain is required before surgery. On the one hand, biliary drain could cause bile contamination; on the other hand, it could restore physiologic bile flow permitting the maintenance of gut eubiosis. The percentage of bile contamination in stented patients was reported to be up to 92% of the samples collected during surgery, while fungal presence was found in 25% of the patients. Fungal presence was directly related to the longer period between biliary drain positioning and surgery[58]. A frequent presence of at least one bacterial species showing antibiotic resistance was also reported, and these patients presented with significantly higher rates of postoperative morbidity[37]. In a large retrospective analysis of 1964 patients undergoing pancreaticoduodenectomy and receiving preoperative biliary drain, 30.8% of them presented biliary contamination with the most common contaminants being *Enterococcus*, *Klebsiella*, and *Enterobacter*.

Postoperative pancreatic fistula (POPF) is the main postoperative complication following pancreatic surgery, and it is related to higher morbidity rates. Bile contamination was an independent risk factor for POPF grade B/C with an odds ratio of 1.33. Furthermore, bile contamination was associated with wound and catheter infections[36]. Similar data were reported in successively published papers[59]. Coppola et al[60] found in the bile different microbes related to different complications: *E. coli*, *Klebsiella pneumoniae* (*K. pneumoniae*), and *Enterococcus faecalis* were prevalent in surgical site infections; *E. coli*, *K. pneumoniae*, *Enterococcus faecalis*, and *Enterococcus faecium* were more abundant in POPF; and *E. coli*, *Enterococcus faecalis* and *Enterococcus faecium* were found in delayed empty gastric syndrome. Abe et al [61] analyzed the cultures of drainage fluid from patients undergoing pancreatic surgery. They found that the presence of *Enterobacter* species, *Enterococcus* species, and *Candida* species was significantly associated with clinically relevant POPF. Furthermore, the presence of *Candida* species resulted in being an independent factor for POPF C and POPF-related hemorrhages[61,62]. On the contrary, in other

studies (with a restricted number of patients), bacteroidia or fungal bile contamination were not reported to be associated with higher POPF rates or different global morbidity and mortality rates[58,63]. Different population samples and geographic bias in defining POPF or in sample collection and analysis could at least partially explain the differences.

Impact of microbiota in chemotherapy response

In the setting of advanced stages, traditional chemotherapy, mainly based on the FOLFIRINOX regimen (5-fluorouracil, oxaliplatin, and irinotecan) or gemcitabine with or without cisplatin or nab-paclitaxel, has a pivotal role. Chemoresistance is one of the most challenging aspects of systemic treatment.

Microbiota affects gemcitabine response thus influencing patients' prognoses. Most of the PanCa-associated abundant bacteria, including *K. pneumoniae* and other species from the *Gammaproteobacteria*, are cytidine deaminase producers. The production of this enzyme results in higher gemcitabine degradation and consequent chemoresistance[30]. Consistently, quinolone administration in patients infected with *K. pneumoniae* allowed for a better prognosis[64]. Nevertheless, gemcitabine use can alter the gut microbiota composition being a potential cause of PanCa progression[65], and the use of antibiotics increases side effects[66]. Adding *Lactobacillus paracasei* improved gemcitabine response in mouse models[67]. Similarly, *Lactobacillus spp.* reduced diarrhea, which is one of the most common side effects of chemotherapy based on irinotecan[42].

Although evidence is still scarce, the use of oncolytic viruses, mostly adenovirus, in combination with gemcitabine may improve its efficacy through different mechanisms including an antitumor immunity booster activity[68].

Other relations between microbiota and response to chemotherapy have been tested for other kinds of solid cancer, and specific data on PanCa are still needed[42].

Impact of microbiota in immunotherapy

Immunotherapy resulted in a game-changer in the treatment of several solid malignancies in the recent decade, and the inhibition of immunological checkpoints has been the most explored strategy for eliciting an antitumor immune response[69,70]. The immune checkpoint inhibitors are monoclonal antibodies targeting molecules, such as the programmed cell death protein 1/programmed death-ligand 1 or cytotoxic T-lymphocyte antigen 4 expressed by tumor or immune cells.

PanCa is one of the cancers for which no immunotherapeutic drugs have been licensed since many clinical trials have failed to show a benefit in terms of response rate and survival[42]. The weak success of the immune checkpoint inhibitor treatment is due to the immunologically "cold" phenotype characterized by the low mutation load and limited expression of neoantigens in PanCa in addition to the immunosuppressive action of the resident stromal cells. Although the fine mechanism of interaction between the microbiota and the immune system in PanCa needs to be examined in-depth, the combination of immune checkpoint inhibitors and chemotherapy could produce promising results. For example, specific polymeric nanoformulations of oxaliplatin and doxorubicin can upregulate the damage-associated molecular patterns expression in PanCa models, activating dendritic cell maturation and adaptive immune response[71]. These two nanoformulations act both by preventing tumor growth and by showing a prophylactic action through inoculation in Pan02 mouse models.

Vaccines are the most effective way to overcome the PanCa hypoimmunogenicity, and nanotechnologies can enhance their immunostimulatory effects[72].

Recent studies have highlighted the importance of stromal macrophages demonstrating the possibility to restore antitumor immunity. The employment of TLR agonists and kinase inhibitors can induce an M1-like polarization. Different PanCa models have been treated with nanoformulations with the ability to reprogram the macrophages phenotype, showing excellent results[73,74].

OTHER IMPLICATIONS OF MICROBIOTA ALTERATIONS AND OTHER FUTURE PERSPECTIVES

Modifying microbiota composition to reduce the risk of PanCa development

As previously reported, several modifiable risk factors have been recognized including smoking habits, alcohol abuse, and diet (high meat intake and low fruit consumption). It is expected that about a quarter of PanCa could be avoided by acting on these factors[9,75]. Since most of them are strictly connected with the microbiota, the possibility to modulate its composition or function could be a promising tool against cancer. There is an ongoing phase II randomized clinical trial (NCT04631445) analyzing the effect of a ketogenic diet in metastatic patients receiving chemotherapy, but unluckily the microbiota evaluation is not included.

A growing number of studies are analyzing the potential role of the so-called "next-generation probiotics" or "live biotherapeutics" that includes short-chain fatty acids producers. These microbes are implied in maintaining the intestinal barrier integrity with the reduction of bacterial translocation and in the reduction of fungal overgrowth[2]. But, to date, specific results of the effects on PanCa are lacking.

In animal models, the 4-wk oral administration of the probiotics *Lactobacillus paracasei* and *Lactobacillus reuteri* alone or combined with an intraperitoneal injection of gentamicin was related to a lower chance of developing precursors of PanCa. Furthermore, they allowed a lower increase of liver enzymes caused by gemcitabine[76]. Similarly, oral administration of the probiotic *Aspergillus oryzae* showed an antitumoral activity. The heptelidic acid was the involved bacterial-produced molecule able to pass the intestinal barrier, reach other organs, and induce apoptosis through the p38 MAPK signaling pathway [77].

In experimental studies with xenografts, Sethi *et al*[50] found that administration of oral antibiotics causing bacterial depletion achieved an antitumor effect through a switch from Th2 immune phenotype toward a Th1 differentiation of CD4+ T cells, with the activation of CD8+ T cells, lower levels of MDSCs, and finally an increase in M1 macrophage differentiation together with lower levels of the protumor IL-17a and IL-10 in the tumor microenvironment. Furthermore, these changes were not seen in T and B cells-deprived animals. Similarly, the administration of oral antibiotics to wild-type mice caused a reduction of the PanCa size by 50% through the reversing of the immunosuppressive tumor microenvironment[28].

Further research about microbial engineering strategies that could allow on-site recruitment of CD8+ T cells *via* interferon- γ production or interaction with the complement cascade is strongly warranted[2].

Despite few specific studies being available, the fecal microbiota transplant through modifying the entire gut microbiota ecology, could represent a great opportunity in PanCa treatment. Experiments in fecal microbiota transplantation animal models confirmed the responsibility of gut microbiota in the modulation of the intratumoral microbiome[78].

Drug delivery systems are bio-responsive elements able to change and thus release drugs in a particular microenvironment (*e.g.*, low level of pH, hypoxia, or presence of specific enzymes). Consequently, the drug delivery systems have been recently proposed as a promising instrument for microbiota modulation through the delivery of pre/probiotics with the capability of depleting protumoral bacteria and eliminating their toxins[79].

However, specific studies are needed to introduce this promising tool in routine clinical practice.

Microbiota as a biomarker of PanCa

Since complete PanCa prevention is not expected, an early diagnosis would be of great help in widening the chance to cure the patients.

Within the species found to be increased/decreased in the saliva of the affected patients compared to the control group, *Neisseria elongata* and *Streptococcus mitis* resulted in a distinguishing signature of PanCa with a sensitivity of 96.4% and a specificity of 82.1% representing a potential biomarker for early cancer detection[23]. In the saliva of the PanCa patients, the ratio of *Leptotrichia* and *Porphyromonas* was reported to be significantly higher compared with the control group[53]. The presence of a high level of serum antibodies against *Porphyromonas gingivalis* was found to be associated with a two-fold higher risk of developing PanCa within 5 years, while high levels of anti-commensal microbe antibodies seemed related to a reduced risk of PanCa[11].

Kim *et al*[80] found that altered human microbiota composition evaluated with microbial extracellular vesicles from blood samples could represent a novel biomarker. Six species, *Ruminococcaceae* UCG-014, *Lachnospiraceae* NK4A136 group, *Akkermansia*, *Turicibacter*, *Ruminiclostridium*, and *Lachnospiraceae* UCG-001, were more abundant, while four species, *Stenotrophomonas*, *Sphingomonas*, *Propionibacterium*, and *Corynebacterium*, were less represented in PanCa patients. With these findings, a prediction model for PanCa was built, and the related area under the receiver operating characteristic curve was 1.000[80].

Furthermore, experiments with spontaneous PanCa in animal models demonstrated that the polyamine metabolism of some gut bacteria including *Lactobacillus* was significantly dysregulated in the very early stages of PanCa[1].

Unfortunately, none of the presented potential biomarkers is available in clinical practice[21]. So, further studies are strongly warranted to validate new diagnostic tools.

Prognostic value of changes in the microbiota of the PanCa patients

One of the most frequently asked questions by patients affected by cancers is about their prognosis. The finding of further prognostic markers, other than the well-known staging systems, could help doctors answer this patient concern.

Riquelme *et al*[78] compared the disparity in microbiota composition of the PanCa tissue of the patients with different prognoses using 16S rRNA gene sequencing. Long-term survivors (alive 5 years after surgery) showed the highest alpha-diversity and a particular signature composed of *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*, and *Bacillus clausii* with an area under the curve of 97.5%. Furthermore, this group of bacteria was associated with greater activation of CD8+ T cells. Furthermore, gut microbiome from short-term survival could induce PanCa onset in a mouse model through the establishment of an immunosuppressive environment suggesting the role of both intrapancreatic and gut microbiome[28,78]. Tumors showing a lower immunosuppressive environment (more neoantigens MUC16 - CA 125 - and CD8+ T cells) confer longer survival rates[81].

Using data from The Cancer Genome Atlas, Chakladar *et al*[51] found that only *Acidovorax ebreus* was linked to a high tumor grade. A significantly higher microbial biodiversity in metastatic and short-survival patients with a predominant percentage of Proteobacteria, particularly *Acidovorax ebreus* and members of the *Gammaproteobacteria*, was also reported. *Citrobacter freundii* and *Shigella sonnei* were associated with the dysregulation of cancer-associated pathways. Furthermore, they found different microbes associated with survival and metastasis. Analyzing The Cancer Genome Atlas database, a prognostic score was proposed by other authors. The high tumor score was associated with p53 mutation, higher tumor mutational burden, and unfavorable and immunosuppressive tumor microenvironment. This high score was found to be related to increased cell proliferation and a higher chance of achieving a positive margin following surgery[82].

In a study with almost 300 PanCa patients, the presence of *Fusobacterium* species was found to be an independent factor of higher mortality[83]. Similarly, the presence of *Pseudomonas aeruginosa* was found to be a negative prognostic biomarker[41].

CONCLUSION

The complex interplay between microbiota and the immune system at different anatomical districts (mostly gut and pancreas/intratumor) might have a role in both the onset and progression of PanCa. Due to the poor prognosis of this tumor despite global advances in surgery and perioperative management, every effort to find new potential targets is welcome. Modifications in microbial composition related to cancer onset could be both a promising target for microbiota shaping and cancer treatment and a potential biomarker for early cancer detection. With the progressive advances in microbiota knowledge, new possibilities for treatment and patient stratification could be expected in the coming years with an improved prognosis for patients with PanCa.

FOOTNOTES

Author contributions: Bartolini I, Nannini G, and Risaliti M contributed to writing—original draft preparation; all the authors contributed to conceptualization and design of the study, critical revision of the article, and final approval of the version of the paper; Taddei A and Amedei A supervised this study.

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