Reducing the Risk of Pancreatic Cancer using Microbiome

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Abstract

In the coming decades, there will likely be an increase in pancreatic cancer mortality. A poor prognosis for this aggressive cancer is caused by late detection and therapy resistance. Harnessing the microbiome may present potential opportunities for diagnostic and therapeutic approaches, according to mounting evidence that host-microbiome interactions play a critical role in the development of pancreatic cancer.

Keywords: Microbiome • Pancreatic cancer • Carcinogenesis

Introduction

Around 496,000 new cases and 466,000 deaths from cancer-related causes are caused by pancreatic cancer each year, making it the 12th most common cancer overall. Demographic shifts are expected to cause these numbers to nearly double by 2040.The prognosis for pancreatic cancer is not good. Modern therapies have only slightly improved the 5-year overall survival rate, which is still just 5–10% and is the lowest of all cancer types. More than 90% of cases of pancreatic cancer are diagnosed as Pancreatic Ductal Adenocarcinoma (PDAC), which develops from the ductal cells that make up the exocrine portion of the pancreas. PDAC has a generally poor prognosis due to a variety of factors, such as the lack of well-established risk factors and prevention methods, the absence of an effective screening tool, the aggressive biology of the tumour, the late diagnosis (typically made at the locally advanced or metastatic stage), and therapy resistance. Resistance to treatment, and nearly made at the locally advanced or metastatic stage. Finding changes in the microbiomes of patients with pancreatic cancer will probably pave the way for the creation of novel screening, diagnostic, and therapeutic methods for this lethal condition. Emerging data suggests that the microbiome influences pancreatic carcinogenesis. The literature on the microbiome and pancreatic cancer is reviewed in this article.

Pancreatic cancer risk factors

PDAC is a prime example of a cancer that is fueled by inflammation. Inflammation is a cause of carcinogenesis and a risk factor for pancreatic cancer .In more than 90% of cases, oncogenic KRAS is the most frequent driver of mutation in human PDAC. Given that KRAS expression is extremely proinflammatory and that pancreatitis length is correlated with a propensity for KRAS mutations, there is a synergistic interaction between KRAS activation and inflammation. Non-modifiable risk factors for PDAC include advancing age, family cancer syndromes, being of the Afro-American race, and having a non-O blood group in addition to chronic pancreatitis, including hereditary and other kinds. The only two modifiable risk factors for pancreatic cancer that have sufficient evidence to be regarded as well-established causes are tobacco use and obesity. An higher risk of pancreatic cancer is also linked to a high-fat diet, diabetes, poor dental health, blood antibodies against specific oral pathogens, and poor oral health status. These risk factors include changes in the human microbiome that may be a common intermediate molecular step leading to pancreatic carcinogenesis, as well as a state of chronic systemic inflammation that may be pro-tumorigenic.

The human microbiome

The microbiota, which is made up of bacteria, viruses, fungi, and protozoa, is a diverse group of microbes that live inside the human body. The phrase "microbiome" primarily refers to microorganisms, their genetic material, and the particular host environment they occupy, while the terms "microbiota" and "microbiome" are currently frequently used synonymously. The gastrointestinal tract, skin, and oral cavity contain the majority of the human microbiota, although organs once thought to be sterile, such the lung, liver, and pancreas, are now known to contain low-biomass microbial communities. It is yet unknown if the microbiomes in these niches are naturally developed or if they a Normal microbiome composition varies greatly across people and between body regions, depending on the environment, host genetics, nutrition, use of antibiotics, and way of life . In a healthy state, commensal microbes collaborate symbiotically with the host at several body sites, contributing to a wide range of physiological activities. Dysbiosis, a disruption of the delicate balance between the microbiome and the host, may have a role in the aetiology of several diseases, including cancer the result of temporary migration of microorganisms from nearby places.

The microbiome in pancreatic cancer

1. **The Intratumoral Microbiome:** A tumour is much more than a collection of abnormally growing cells, despite the fact that cancer is traditionally thought of as a genetic disease. Instead, the Tumour Microenvironment (TME) is made up of a variety of unique cell types that interact with one another in a complicated manner, aiding in the acquisition of defining characteristics that promote tumour growth and the spread of metastatic lesions. One could anticipate that the interaction between bacteria and tumour cells will be able to influence oncogenesis because the microbiome is an intrinsic part of the tumour microenvironment. The first instance of intratumoral bacteria was discovered more than a century ago. At least 33 main cancer types currently provide significant evidence of an intratumoral bacterial microbiome. In seven different cancer forms, including pancreatic cancer, Nejman et al. directly examined the bacterial communities of tumours and the surrounding normal tissues. They found that each tumour type had a unique microbiota compositionIn 76% of the tumours and 15% of the normal tissues, bacterial DNA was found by Geller et al. when they examined pancreatic tumour tissues with normal pancreatic tissues Gammaproteobacteria, which includes members of the Enterobacteriaceae and Pseudomonadaceae, were found to be the most prevalent species, with *Pseudomonas*, *Citrobacter, Klebsiella, Streptococcus*, and *Acinetobacter* having the greatest mean relative abundances. These numbers agree with those provided by Nejman et al. Contrarily, Riquelme et al. discovered that the human gut microbiome only makes up around 25% of the PDAC microbiome while being completely absent from the normal surrounding tissue . This finding raises the possibility that gut microbes only colonise pancreatic tumours. Additional analyses of the intratumoral microbiome revealed tumour enrichment in *Pseudomonas*, *Herbaspirillum*, and *Sphingomonas* as well as *Lactobacillus* spp., *Akkermansia muciniphila*, and *Bacteroides* .

2. **The gut microbiome and pancreatic cancer:** A growing amount of research has linked pancreatic cancer to alterations in the gut flora. The structure of the gut microbial communities of pancreatic cancer patients is obviously different from that of healthy controls, as

assessed by beta diversity analysis, according to studies looking into the relationship between the gut microbiome and pancreatic cancer. Reports on the gut microbial alpha diversity in pancreatic cancer patients are contradictory, with some research indicating higher, similar, or lower diversity in comparison to that of healthy controls. In general, microbial biomarker species may accurately differentiate between PDAC patients and healthy controls. A dysbiosis of the gut microbiome was described in Nagata and colleagues' international study, and significant relationships between PDAC and 30 gut bacterial species were found .These bacterial fingerprints were highly effective at predicting PDAC in the Japanese discovery cohort as well as in the independent patient cohorts from Spain and Germany. All of these cohorts shared the enrichment of Streptococcus and *Veillonella spp.* and the loss of *Faecalibacterium prausnitzii* as PDAC gut microbial signatures. The gut microbial community of PDAC patients had a lower abundance of helpful microbes, such as butyrate-producing bacteria, and a higher abundance of lipopolysaccharide-producing bacteria, according to a Chinese cohort study comparing the faecal microbiome of PDAC patients with that of matched healthy controls. As a result, a notable decrease in Firmicutes, particularly those that produce butyrate, was also noted in the gut microbiota of PDAC patients. A higher 0incidence of pancreatic head cancer than pancreatic body/tail cancers has been theorised to be related to changes in the duodenal milieu. The relationship between the duodenal microbiome and pancreatic cancer has not been extensively studied. The microbiome of several pancreatic locations seems to resemble the microbiota of the same participants' duodenum. The microbial profiles of patients with PDAC have recently been revealed to be altered, displaying elevated levels of bacterial and fungal DNA, decreased microbial diversity, and an enrichment in Bifidobacterium. Additionally, bacteria from the genera Fusobacterium, Rothia, and Neisseria were added to duodenal fluid samples taken from short-term PDAC survivors. It may be worthwhile to pay more attention to microbial profiling of duodenal fluid obtained by endoscopy in order to assess and categorise the risk of pancreatic cancer. Proton-pump inhibitor use is one such factor that can affect the composition of the duodenal fluid. Although there is still debate over *Helicobacter pylori's* function in PDAC, it is probable that changes in duodenal fluid are related to infection of the gastric body mucosa and subsequent hypochlorhydria. Duodenal fluid samples collected from short-term PDAC survivors also included bacteria from the genera Fusobacterium, Rothia, and Neisseria. To determine and classify the risk of pancreatic cancer, it may be beneficial to pay closer attention to the microbiological profiling of duodenal fluid acquired by endoscopy. Use of proton-pump inhibitors is one such element that may have an impact on the duodenal fluid's makeup.The role of Helicobacter pylori in PDAC is still up for question, but it is likely that alterations in duodenal fluid are connected to infection of the gastric body mucosa and the ensuing hypochlorhydria. The stage of the malignancy was strongly linked with the relative quantity of Cyprinivirus. Bacteriophages, which infect particular bacterial species and support the maintenance of a balanced gut microbiome, make up a major portion of the enteric virome. In the gut microbiome of patients with PDAC, Streptococcus oralis, *Streptococcus parasanguinis*, *Veillonella atypica*, and *Veillonella parvula* were among the 58 bacteriophages that Nagata et al. discovered. There may be synergistic pathogenic interactions, whereby virome dysbiosis promotes the formation and persistence of opportunistic microorganisms that can influence the progression of cancer. Before contemplating phage therapy as a possible treatment for pancreatic cancer, the gut phageome must first be characterised.

The oral microbiome and pancreatic cancer

Regarding the gut microbiome, various studies have examined the relationship between pancreatic cancer and the oral microbiome. Despite some research finding greater alpha diversity in the oral microbiota of pancreatic cancer patients, the bulk of investigations, including those with higher sample sizes, found no changes in alpha diversity between cancer patients and controls. Additionally, while some research demonstrate that it is possible to discriminate between the general structure of the oral microbiome in pancreatic cancer patients and that of healthy control participants other studies fail to find such changes. Nevertheless, there is evidence suggesting the oral microbiome contributes to the aetiology of pancreatic cancer, some of which originated from the idea that the link between periodontal disease and pancreatic cancer is caused by alterations in the oral microbiota. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, two microorganisms involved in chronic periodontitis, were linked to an elevated risk of pancreatic cancer in a major study by Fan and colleagues, which included mouth wash samples from patients in the USA. These findings are consistent with earlier studies' findings that PDAC risk was increased in patients with high plasma levels of antibodies to *P. gingivalis*. However, Porphyromonas was found in similar amounts in cases and controls in a study of 273 cases of pancreatic cancer and 285 controls from Iran, and it was not linked to pancreatic cancer. It's interesting that the authors of this study found that having more *Haemophilus* was linked to a lower risk of pancreatic cancer, which supported earlier findings in a population from the USA.

Mechanisms linking the microbiome to pancreatic cancer

Through a number of ways, the microbiome can influence the development of cancer, both locally and remotely. These include the generation of DNA damage, the promotion of chronic inflammation, the modification of the tumour immunological milieu, and the stimulation of oncogenic signaling pathways. By attaching to, invading, or injecting virulence factors into the host target cell, secreting poisons and microbial metabolites, or by metabolising host and food metabolites, microorganisms can affect carcinogenesis.

Mendez et al. examined the gut microbiome and metabolome in a genetically modified PDAC mice model to assess the microbial metabolites influencing pancreatic carcinogenesis. They demonstrated that the gut microbial community changed as PDAC progressed and, by analysing the metabolome of the involved bacterial species, discovered chemicals involved in polyamine metabolism. Patients with PDAC validated the findings of higher serum polyamine levels when tumours developed in mice. Butyrate and pyridoxine are two more microbe-derived metabolites that may be protective against the onset of cancer. Short-chain fatty acids (SCFAs), such as butyrate, have been shown to have anti-inflammatory and anti-neoplastic activities when generated by specific bacteria from the fermentation of non-digestible carbohydrates. Butyrate was discovered to have "pro-differentiating, anti-proliferative, anti-invasive, pro-apoptotic" and chemo-sensitizing actions in PDAC cell lines *in vitro* in the setting of pancreatic cancer. Additionally, sodium butyrate lessens the desmoplastic response in PDAC by preventing the activation of pancreatic stellate cells. Microbe-induced inflammation may intensify pancreatic oncogenic signaling because KRAS mutant signalling alone is insufficient to start invasive PDAC. Toll-Like Receptor 4 (TLR4), Toll-Like Receptor 7 (TLR7), Nod-Like Receptor (NLRP3) inflammasome , and Dectin are examples of pattern recognition receptors that may be locally activated by microbes and may enhance mutant KRAS signalling and hasten pancreatic oncogenesis. In both early and advanced PDAC, activation of TLR2 and TLR5 was found to decrease both innate and adaptive immunity.

In addition to influencing genetic oncogenic processes, the intratumoral microbiome may potentially influence the creation of an immunosuppressive microenvironment that favours the growth of pancreatic cancer. By inducing a systemic inflammatory response or by getting to the pancreas (either through the bloodstream or the gastrointestinal tract) and locally modulating inflammation and the immune response, bacteria distant from the pancreas, like those in the gut and oral microbiomes, may promote pancreatic carcinogenesis. The extensive immunosuppressive tumour microenvironment that pancreatic cancer flourishes in contributes to its aggressive biology. A highly fibrotic stroma that frequently has pro-tumor immune suppressor cell infiltration, such as that of Tumor-Associated Macrophages (TAMs), regulatory T cells (Tregs), and Myeloid-Derived Suppressor Cells (MDSCs), characterizes tumours . The collagen that makes up the dense desmoplastic stroma of pancreatic tumours is produced by myofibroblast-like Pancreatic Stellate Cells (PSCs) and cancer-associated fibroblasts (CAFs). PSC activation may be influenced by TLR9 bacteria-induced stimulation Neoantigens in pancreatic cancer tumours from long-term survivors are many and diverse, and they are linked to higher levels of CD8+ T cell infiltrates, as shown by research by Balachandran et al. It's interesting that the neoantigens showed similarities to peptides from infectious agents, which is consistent with the idea that tumour neoantigens and microbial epitopes exhibit molecular mimicry. These findings imply that tumour immunogenicity and patient outcomes may be influenced by microorganisms. Despite the fact that PDAC tumours express neoantigens that T cells can recognise, there are adaptive immune suppression mechanisms that prevent T cells from engaging in

lethal action. Most intracellular bacteria are located in the cytoplasm of immunological and tumour cells. Cell motility, extracellular matrix interaction, complement cascade, and PD-1 signaling are only a few of the important processes they modulate in relation to immune activity and cancer hallmarks. It's interesting that the tumour microbiome seems to have a dual effect because it can either enhance immune activation or repression. Pushalkar et al. revealed that microorganisms promote intratumoral immune suppression mediated by TLR ligation, contributing to the progression of pancreatic cancer using genetically engineered animal models. A decrease in pro-tumoral MDSCs and M2 macrophages and a rise in intratumoral T cells and antitumoral M1 macrophages were caused by immunogenic reprogramming of the PDAC microenvironment, which protected against PDAC progression.

The microbiome and treatment responses in pancreatic cancer

It is becoming more and more clear that the microbiota affects how well cancer treatments work. However, the relationship between the medicines and the microbiota is dynamic and bidirectional. The microbiome can influence drug metabolism and absorption, altering the effectiveness and negative effects of PDAC therapy, and pharmaceuticals can also alter the host's microbiome.

1. **Chemotherapy:** Chemotherapy drugs like gemcitabine are frequently used to treat PDAC. Gammaproteobacteria, which are incredibly common bacteria in human PDAC, have been demonstrated to be able to metabolise gemcitabine to make it inert. When antibiotics were administered directly into the tumour in a mouse model of colon cancer, gemcitabine-induced apoptosis was dramatically increased, pointing to a role for intratumoral bacteria in gemcitabine resistance. However, gemcitabine-induced gut dysbiosis may paradoxically decrease the drug's anti-cancer effects and increase both local and systemic inflammation. Gemcitabine treatment resulted in an overall rise in pro-inflammatory bacteria in the stomach in a PDAC xenograft mouse model, but Lachnospiraceae and Ruminococcaceae, two bacterial families recognised for their capacity to produce butyrate, decreased. The anti-inflammatory drug inosine and its metabolites xanthine and hypoxanthine were significantly reduced in serum during treatment with gemcitabine, which is probably related to the observed dysbiosis.

2. **Immunotherapy:** With the possible exception of very uncommon tumours with high microsatellite instability, immunotherapy with immune checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4, has been ineffective for pancreatic cancer thus far. In distinct types of epithelial tumours, commensal gut bacteria were discovered to positively influence the effectiveness of PD-1-based immunotherapy, with non-responders displaying an imbalance in gut microbial composition that was connected with reduced immune cell activation. It is thought that Bifidobacterium, one of the primary genera in the human gut microbiome, increases the effectiveness of immune checkpoint blockers.

Microbiome modulation in pancreatic cancer

The majority of pancreatic cancer patients have advanced, incurable illness when they first present, and gemcitabine-based palliative chemotherapy is the mainstay of treatment. Neoantigen vaccines and genomic targeted therapeutics are two novel therapeutic approaches that have demonstrated variable efficacy in PDAC.

1. **Diet:** Dietary modifications are a desirable strategy for influencing the microbial communities in the gut. A high-fat diet causes gut dysbiosis, which is characterised by gut inflammation and increased permeability, as well as a decrease in the abundance of Bacteroidetes and an increase in Firmicutes and Proteobacteria . Bacteria and their byproducts may also move from the gut into the bloodstream. On the other hand, a diet high in fibre may prevent cancer because it boosts microbial synthesis of butyrate and other anti-inflammatory and pro-apoptotic SCFAs.

2. **Probiotics:** According to their definition, probiotics are "live microorganisms that, when administered in sufficient amounts, confer a health benefit on the host." [The variety of microorganisms with potential health advantages is expanding in tandem with the rising information on the human microbiome. Probiotics have been proposed as a strategy for both cancer prevention and treatment, although inconsistent outcomes have been found in a number of studies. A reduction in the number of butyrate-producing bacteria is a common feature of gut dysbiosis in PDAC patients.

3. **Antibiotics:** The use of antibiotics to eradicate microbes in cancer is debatable; at the moment, only the eradication of *H. pylori* in gastric carcinoma and MALT lymphoma is advised. Antibiotics may be helpful in the treatment of PDAC, according to preclinical studies that reveal a decreased rate of tumour growth and enhanced responses to anti-PD-1 immunotherapy and gemcitabine. The use of antibiotics in patients with metastatic PDAC was associated with improved survival in those undergoing gemcitabine-based chemotherapy, potentially as a result of improved microbiota modulation and a reduction in local and systemic infections. Antifungal medications were also discovered to reduce the growth of PDAC and enhance treatment response. Antibiotic use over an extended period of time may have negative consequences, including drug toxicity, systemic microbial dysbiosis.

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