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REVIEW

Impact of gut microbiome in the development and treatment of pancreatic cancer: Newer insights

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Abstract

The gut microbiome plays an important role in the variation of pharmacologic response. This aspect is especially important in the era of precision medicine, where understanding how and to what extent the gut microbiome interacts with drugs and their actions will be key to individualizing therapy. The impact of the composition of the gut microbiome on the efficacy of newer cancer therapies such as immune checkpoint inhibitors and chimeric antigen receptor T-cell treatment has become an active area of research. Pancreatic adenocarcinoma (PAC) has a poor prognosis even in those with potentially resectable disease, and treatment options are very limited. Newer studies have concluded that there is a synergistic effect for immunotherapy in combination with cytotoxic drugs, in the treatment of PAC. A variety of commensal microbiota can affect the efficacy of conventional chemotherapy and immunotherapy by modulating the tumor microenvironment in the treatment of PAC. This review will provide newer insights on the impact that alterations made in the gut microbial system have in the development and treatment of PAC.

Key Words: Pancreatic cancer; Gut microbiome; Chemotherapy; Dysbiosis; Intratumoral microbiome; Gut flora

Core Tip: Pancreatic cancer (PC) remains of on the most dismal in terms of prognosis. Treatment options are limited and even after complete surgical resection, the prognosis remains poor. The gut microbiome has been incriminated in the past for the development of certain cancers. Our review found that observation to be true as well for PC. Furthermore, we also found that it plays a role in efficacy and tolerance of certain regimens used to treat PC.

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INTRODUCTION

Pancreatic cancer (PC) usually refers to ductal pancreatic adenocarcinoma (PAC) (including its subtypes), which represents 85 to 90 percent of all pancreatic neoplasms. PC ranks fourth among cancer related mortality in the United States, only behind lung, colorectal, and prostate cancers in males, and lung, breast, and colorectal cancers in females. Although the incidence of PC has been relatively stable over time, the increasing use of imaging techniques such as endoscopic ultrasound and helical (spiral) abdominal computed tomography (CT) scans has revealed an increasing number of incidentally found cases of PC[1,2].

PC can run in some families, and approximately 10 percent of individuals with PC have a family history of the disease[3,4]. There are two broad categories of hereditary risk for PC which are inherited genetic predisposition syndromes associated with PC and familial PC (FPC), which is defined as a family with a pair of affected first-degree relatives who do not meet criteria for a known PC-associated genetic predisposition syndrome[5].

The major gene causing most cases of hereditary PC remains unknown. Pathogenic germline variants (PGVs) in the breast cancer associated (BRCA) 1 and 2 genes are the most commonly associated mutations, occurring in 13 to 19 percent of FPC families[6]. Next generation sequencing helped uncover other genes causing hereditary pancreatic ductal adenocarcinoma: The partner and localizer of BRCA2 (PALB2) gene and the ataxia-telangiectasia mutated (ATM) gene[7,8]. PGVs are especially common in individuals with early onset PC (*i.e.*, developing before age 50)[6]. Cigarette smoking contributes to the risk of PC in patients with hereditary pancreatitis and FPC and is associated with an earlier PC diagnosis by approximately 20 years[9].

In recent years, the role of gut microbiome in the development and treatment of several cancers, including PC, has been an area of active research. *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and even *Helicobacter Pylori* (*H. Pylori*) are linked to an increased risk of PC[10,11]. Probiotics have been shown to be effective in reducing pancreaticoduodenectomy complications, by directly suppressing the growth of cancer cells. Postbiotics have been shown to have selective cytotoxicity against tumor cells. Prior literature revealed that fecal microbiota transplantation led to a reduction in tumor size for PC[12].

Carcinoembryonic antigen-related cell adhesion molecule 7 (CEACAM-7), also known as CGM2, is a glycoprotein expressed on the luminal surface of epithelial cells near the mouth of colonic crypts and on pancreatic ductal epithelial cells[13]. Most recently it has been shown that CEACAM7-directed chimeric antigen receptor (CAR) T cells can effectively mediate remission of late-stage patient-derived PAC xenograft tumors[13].

This review will provide a concise and up to date overview of the impact of commensal gut microbiota in the development and management of PAC. Furthermore, we will focus on the pathophysiology and pathogenesis by which the gut flora can gain oncogenetic attributes and to what extent their alteration can affect the treatment and outcome of PAC.

DIAGNOSIS OF PC

Recent advances in imaging techniques have elevated the diagnostic acumen for PC. Abdominal ultrasound (US) is a non-invasive approach, which can detect pancreatic masses with an accuracy of 50%-70%[14]. Although there are no tell-tale characteristic signs of different pancreatic masses, a hypoechoic mass, pancreatic and/or biliary duct dilation could point towards an ominous pathology[14,15]. If a contrast enhanced US is available, the diagnostic accuracy could be significantly enhanced as hypovascularity of a mass point towards PAC whereas endocrine cell tumor is hyper vascularized and any pancreatitis associated mass is usually iso-vascularized[14,16].

CT with contrast is perhaps the most widely used-in detection and staging of PC. Hypovascularity, increased fibrous stroma, and decreased enhancement compared to surrounding tissue points towards PAC[17]. In hypoattenuating lesions and in instances where CT is equivocal, multi-detector row CT can be helpful as it provides three dimensional images and various phases of contrast enhancement-parenchymal, portal venous, and arterial-leading to earlier detection and accurate staging of the cancer [18-20]. Enhanced magnetic resonance imaging (MRI), due to better soft tissue visualization, has been shown to be equal or superior to CT imaging for blood vessel invasion and local extent, however, it is poor in detecting the involvement of portal venous system or duodenum[21-23]. The most accurate and sensitive method for detection of even the smallest tumors with or without vascular invasion is EUS-superior to MRI, CT, or US. It is also an excellent modality for diagnosis when combined with biopsy and has incredibly high sensitivity to detect metastasis to the lymph nodes as well as vascular invasion [24-27]. The biggest challenge in diagnosis is differentiating between chronic pancreatitis and PAC, this is when EUS with biopsy comes in handy.

STAGING OF PC

The staging of PC at the time of diagnosis is pivotal for prognosis and treatment planning as the aggressive or palliative care approach could be applied based on the stage. The role of CT imaging with contrast is pivotal in determining the stage, however, sometimes, sophisticated modalities such as enhanced MRI, EUS, or fluorodeoxyglucose-positron emission tomography could be needed. The tumor size, location in the pancreas, surrounding structures involvement-with or without vascular involvement, and spread to surrounding lymph nodes or metastasis are the components involved in staging for PC.

The T (tumor), N (Node), and M (Metastasis) is the widely accepted staging systems for PC as per The American Joint Committee for Cancer[28]. The T stage is classified based on the tumor size within the pancreas and/or involvement of vascular structures. The N and M stage is classified based on the involvement of regional lymph nodes and sites of metastasis, if any. Subsequently, based on the imaging, cancer is characterized as resectable, borderline resectable, locally advanced, or metastatic disease. Stages I and II do not involve any major blood vessels, stage III is a localized tumor but with involvement of a major blood vessel, whereas Stage IV is metastatic disease[28].

The National Comprehensive Cancer Network stages PC primarily based on tumor extent. This is primarily in the absence of metastatic disease and resection options are localized advanced/unresectable, borderline resectable, and resectable disease. Locally advanced/unresectable disease is predominantly when the tumor involves major vascular structures such as aorta, superior mesenteric or portal vein (unreconstructable), or > 180 degrees of tumor contact with the Superior mesenteric artery or celiac artery. Resectable disease or borderline resectable is defined as no involvement of any vascular structures mentioned above or ≤ 180 degrees of involvement[29].

PC-MODALITIES OF TREATMENT

Depending on the staging of PC, there are various modalities which are employed for the treatment. Surgical resection is always desirable, however, due to the relatively silent clinical course of PC, only 1/5th of patients have resectable tumors at the time of diagnosis[30,31]. The most utilized surgical procedures are total pancreatectomy, distal pancreatectomy, and Whipple's procedure depending on the staging of the cancer[32]. Previously, in patients presenting with jaundice, preoperative biliary stenting was considered if there was a tumor on the head of the pancreas causing biliary obstruction, however, recent studies have shown that this modality is associated with increased time to surgery, increased rates of infection, and complications; preoperative biliary stenting is as a result, no longer recommended for head of the pancreas tumors which have not metastasized and can be easily resected [33,34]. However, preoperative stenting can be considered in patients who are undergoing neoadjuvant chemotherapy, if surgery is postponed by logistical constraints, or have severe jaundice[33,34].

In patients who present with PC s of 'borderline resectability', neoadjuvant therapy prior to surgical resection is a consideration. However, data is conflicting. While there is some evidence on increased survival amongst borderline resectable tumors with neoadjuvant gemcitabine-based chemotherapy, there are also studies which suggest an increased postoperative stay and increased surgical challenges in locally resectable tumor patients who received neoadjuvant chemotherapy[35-37]. Also, it is important to note that histological diagnosis is mandatory prior to starting the chemotherapy, which may further delay the time to surgery.

The overall prognosis of PC is abysmal, even post complete surgical resection. As a result, 5-Fluorouracil (with Leucovorin) or Gemcitabine adjuvant chemotherapy is frequently employed post-surgical resection. Which agent is better though, does remain a topic of discussion. Studies are equivocal with some showing no difference between the two whereas others favor gemcitabine[38]. In patients with metastatic disease, the armamentarium consists of psychosocial support, chemotherapy, treating a

variety of other comorbid conditions, and targeted therapy. As far as chemotherapy is concerned in such a setting, Gemcitabine has been shown to be superior, by far and remains the first line standard of care[39]. Arguably, Conroy *et al*[40] have proven that FOLFIRINOX can super side Gemcitabine, as patients on FOLFIRINOX demonstrated not only a better response rate, but also improved one year, progression free, and overall survival[40]. In patients who are non-tolerant to first line gemcitabine, second line treatment consisting of oxaliplatin with fluoropyrimidines have demonstrated some clinical benefit[41,42]. Furthermore, if FOLFIRINOX was used as the first line, gemcitabine-based therapy should be tried as second line and has some clinical evidence of being beneficial[40].

Newer modalities of treatment include but are not limited to the use of epidermal growth factor receptor (EGFR) inhibitors. Medications like Cetuximab and Erlotinib which target the EGFR have been developed recently for targeted therapy and have been shown to be effective in many clinical trials. A combination of gemcitabine with Erlotinib is shown to increase overall survival rates and decrease the progression of PC[43]. PC cells are notorious to adapt in order to decrease the drug delivery to them by production of desmoplastic stroma and lead to resistance to chemotherapeutic agents[44]. Several therapies have recently been developed to decrease this stromal tissue and improve drug penetration despite the desmoplastic stroma, including nab-paclitaxel[45].

Radiation therapy has a somewhat beneficial role alongside surgery and chemotherapy. Neoadjuvant radiation therapy for PC has been described in prior literature. Pisters *et al*[46] demonstrated that minimal toxicity and a very small recurrence rate can be obtained with preoperative fractionation chemoradiation based on 5-Fluorouracil, Whipple's procedure, and intraoperative radiation[46]. In another study, utilizing a similar strategy for treatment but replacing 5-Fluorouracil with paclitaxel-based chemotherapy, the results were similar, however, the toxicity levels were higher[47].

To improve the patient's overall prognosis, radiation therapy is frequently being utilized for management of PC alongside chemotherapy. In the United States, adjuvant radiation therapy is a common norm after the Gastrointestinal Tumor Study Group's prospective study in 1985. Patients with resectable PC were enrolled in this trial and were found to have a significantly longer and medial survival rate when treated with adjuvant chemoradiation[48]. Owing to this trial, adjuvant chemoradiation, the most commonly used adjuvant treatment for patients with resectable PC, is being practiced to date in the United States.

Novel techniques like stereotactic body radiotherapy have also been developed in recent years for targeted delivery of radiation. However, it has only been shown to slow local progression of the disease but has no effect on overall survival rates as the majority of mortality in PC patients is secondary to systemic and distant metastasis[49-51]. As PC is genetically a heterogeneous malignancy, there have also been baby steps in personalized chemotherapeutic regimen based on the patient's genome to significantly increase the rates of chemotherapeutic efficacy by decreasing the resistance and making the response to chemotherapy consistent across all individuals. However, further research is needed on this novel therapeutic approach.

GUT MICROBIOTA AND PC

Mechanisms via which microbes regulate pancreatic oncogenesis

The gut microbiome, which refers to microbes naturally present in the human mucosal surfaces, has shown, when altered, to lead to oncogenesis and to some extent affect the response to therapy of several cancers, among which PAC[52]. The exact mechanisms by which oral and intestinal microbiota reach the pancreas remains unknown, but the proposed mechanisms involve the translocation *via* biliary/pancreatic ducts or through the blood circulation[52]. A summary can be found in Table 1.

P. gingivalis, which is a bacterium mainly found in the mouth and associated with periodontal diseases, has shown the ability to disseminate and affect immune response. *P. gingivalis* infection has shown an involvement of toll-like receptors (TLRs) including TLR4, involved in protective immunity. TLR signaling, especially TLR4, has been shown to play an important role in human pancreatic tumors [53]. Furthermore, periodontal diseases, such as the ones caused by *P. gingivalis* can lead to an increased production of nitrosamines[54]. Nitrosamines can be metabolized by Cytochrome P450 and produce electrophiles that can effectively interact with the DNA and lead to the formation of DNA adducts that have a carcinogenic potential if not repaired[55]. Porphyromonas Peptidyl Arginine Deaminase (PPAD) is a protein produced by *P. gingivalis* that has been associated with cancer development by the way of P53 activity and KRAS (Kirsten-ras) mutation[52]. P53, which is a tumor suppressor gene, if mutated can lead impairment of cell cycle arrest and decrease of apoptosis increasing the risk of malignancy. KRAS, which is an oncogene with hydrolyzing effect on guanosine triphosphate, can lead uncontrolled and inappropriate cell proliferation, thus increasing the risk of malignancy[52]. P53 is a transcription factor that can activate the transcription of numerous genes, including the Cyclin-dependent kinase (CDK) inhibitor p21.

P53 is rapidly degraded and therefore not detectable within the cell. Mutation of the P53 gene results in a protein that fails to bind DNA effectively. Therefore, expression of the CDK inhibitor P21 gene is decreased, and P21 protein production is decreased. P21 protein is not available to stop the entry of the

Table 1 Gut microbiota associated with Pancreatic oncogenesis

Bacteria	Primary site	Potential mechanism	Subsequent effect	Ref.
Porphyromonas gingivalis	Mouth	TLR signaling disruption; Nitrosamines production; PPAD production	Loss of protective immunity; DNA adducts formation; P53 overactivity (loss of apoptosis); KRAS mutation (cellular overproliferation)	[52-55]
Aggregatibacter actinomycetemcomitans	Mouth	Nitrosamine production; DNA double-strand breaks; CagE production	DNA adducts formation; genome instabilities; dysregulation of DNA methylation expression	[52, 58,59]
Fusobacterium nucleatum	Mouth	FadA production; Fap2 production	activation of the Wnt/β-catenin pathway; suppression of the cytotoxic effects of NK cells and lymphocytes	[59, 61-63]
Helicobacter Pylori	Stomach	cagA, cag PAI and vacA production	Disruption of host intracellular signaling pathways	[64]
Bacteroides fragilis, Bacteroides vulgatus, Listeria monocytogenes, Clostridium, Lactobacillus, Bifidobacterium	Large bowel	Transformation of primary bile acids to secondary bile acids	Reduction of susceptibility to apoptosis, induction of inflammatory mediators, and perturbation of membranes and cellular movement	[76]
Escherichia coli	Large bowel	Polyamines production	Polyamines upregulation	[81-83]

TLR: Toll-like receptor; PPAD: Porphyromonas Peptidyl Arginine Deaminase; CagE: Cytotoxin-associated gene E; NK: Natural killer; PAI: Pathogenicity island; cagA: Cytotoxin-associated gene A.

cell into S phase, again resulting in unregulated cell cycle progression, potentially leading to carcinogenesis[56]. The KRAS gene, an oncogene, is one of the most frequently mutated genes in PC. This gene is the human homolog of a transforming gene isolated from the Kirsten rat sarcoma virus, hence the name KRAS. Mutations in this gene, the vast majority of which are at codon 12, are activating, leading to abnormal activation of the protein product of the gene[57].

A. actinomycetemcomitans is also an oral microbiome that has been incriminated in PAC[52]. Similar to *P. gingivalis*, it can lead to periodontal infections and lead to increased nitrosamine production[54]. *A. actinomycetemcomitan* can also induce DNA double-strand breaks in host cells, independently of apoptosis, and cause the risk of genome instabilities and subsequently increase the risk of carcinogenesis[58]. Furthermore, the bacteria can produce the cytotoxin-associated gene E (CagE). CagE may have helicase activity, and its role in regulating DNA methylation expression is considered as possible mechanisms of tumorigenesis. CagE gene has been widely expressed in various cancer cell lines and cancer tissues including PC[59]. *Fusobacterium nucleatum* (*F. nucleatum*), which is another oral microbiome produces Fusobacterium adhesin A (FadA), that showed capacity of binding to host cells and is also the most characteristic virulence factor of *F. nucleatum*[59]. The host receptors for FadA are members of the cadherin family, mainly E-cadherin and vascular endothelial (VE) cadherin (CDH5) [60]. FadA binds to E-cadherin of epithelial cells, leading to phosphorylation and internalization of E-cadherin on the membrane; afterwards, canonical Wnt pathway is activated, accompanied by decreased phosphorylation of β-catenin, which accumulates in the cytoplasm and translocate to the nucleus[59]. Increase in Wnt signaling activity and subsequent activation of the Wnt/β-catenin pathway, has shown to be essential in the initiation of PC[61,62]. Furthermore, FadA binds VE-cadherin on VE cells, increasing endothelial penetrability[59]. Therefore, FadA not only directly invades host cells but also allows dissemination of itself and other bacteria into blood by increasing endothelial permeability[59]. *F. nucleatum* can produce a protein called familial adenomatous polyposis 2, which binds and interacts to human inhibitory receptor T cell immunoreceptor on natural killer (NK) cells and lymphocytes. Thus, suppressing the cytotoxic effects of NK cells and lymphocytes, leading to protection of tumors from the immune system and fostering a flourishing inflammatory context[63]. By a mechanism similar to *P. gingivalis*, *F. nucleatum* can be involved with the TLRs and lead to carcinogenesis as discussed previously [53].

H. Pylori is notorious for its association with gastric cancer and yields various virulence factors that may disrupt host intracellular signaling pathways and lower the threshold for neoplastic transformation. Of all virulence factors, cytotoxin-associated gene A and its pathogenicity island (cag PAI) and vacuolating cytotoxin A are the major pathogenic factors[64]. Whether *H. Pylori* infection is associated with PAC remains controversial with conflicting data in the literature. A study by Kumar *et al*[65] showed a very low incidence of *H. Pylori* among patients with PAC, whereas studies by Hirabayashi *et al*[66], and Nilsson *et al*[67] found an association.

Several members of the gut microbial community (especially of the large bowel), including *Bacteroides fragilis*, *Bacteroides vulgatus*, *Listeria monocytogenes*, *Clostridium*, *Lactobacillus*, *Bifidobacterium*, and *Escherichia*, are involved in the transformation of primary bile acids to secondary bile acids, either by

deconjugation, oxidation, dehydroxylation, or epimerization[68-70]. Bile acids have multiple nuclear receptors, including farnesoid-X-receptor (FXR), liver-X receptor, CAR, vitamin D receptor (VDR), pregnane X receptor (PXR), and a non-nuclear receptor Takeda G Protein-Coupled Receptor 5/G-protein-coupled bile acid receptor (TGR5), that may impact carcinogenesis[71,72]. Secondary bile acids can behave as both pro- and anti-carcinogens, depending on the cancer concerned and the concentration of the bile acid present[71-73]. Furthermore, bile acids can modulate the composition of the microbiome and facilitate bacterial translocation into tissues, which is a key step in the carcinogenesis of PAC[74]. Bile acid levels have been shown to be elevated in PAC[75]. Bile acids can also affect risk factors for PAC such as pancreatitis and bile acid efflux disorders, type II diabetes, obesity, and hyperlipidemia; and they can reduce susceptibility to apoptosis, induce inflammatory mediators, and may perturb membranes and cellular movement[76]. A secondary bile acid, deoxycholic acid can bind to TGR5 and activate EGFR, mitogen-activated protein kinase, and signal transducer and activator of transcription 3 signaling in PAC cells, inducing cell cycle progression[77]. Other bile acid receptors such as VDR, FXR and PXR are also found to be highly expressed in PAC tissues compared to normal tissues[78-80].

Polyamines can be produced, accumulated, or used by the following gut bacteria *Escherichia coli* (*E. coli*), *Enterococcus faecalis* (*E. faecalis*), Staphylococcus aureus, Haemophilus influenzae, Neisseria flava, Pseudomonas aeruginosa, Campylobacter jejuni, Yersinia pestis, Vibrio cholerae, Bacteroides dorei, Bacteroides thetaiotaomicron, *Bacteroides fragilis*, Bacillus subtilis, and Proteus mirabilis[81,82]. A mouse study revealed that bacterial polyamine biosynthetic capacity was upregulated and aggravated by tumor progression in PAC and there was a correlated elevated serum level of polyamines[83].

As evidence by the work of Riquelme *et al*[84], Fecal Microbiotal Transplant from human subjects to mice, yielded from PC long term murine survivors, showed a significant reduction in tumor growth, however, that effect was lost with the use of antibiotics altering the fecal microbiota[84,85]. Furthermore, it was found that long term survivor mice that did not receive antibiotics were rich in CD8+ T-cell, enhancing the tumor immune cell infiltration. On the other hand, mice that were treated with antibiotics, thus altering the fecal microbiota, showed an increased number of CD4+FOXP3+ T-regs and myeloid derived suppressor cells which are well known to lower the immune system, thus promoting tumor growth[84,85].

NK cells are a group of cells that play an important role by mediating tumor initiation and progression. NK cells are often found in the circulation, preventing tumor cells from metastasizing[86,87]. When a patient is NK cells depleted, tumor escape and growth may ensue[86]. NK cells having the ability to inhibit CD8+ T cell responses during chronic infections, it has been hypothesized that NK cells can facilitate solid tumors infiltration, among which PC[86].

Hepatotropic viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV) have been incriminated in pancreatic oncogenesis. HBV and HCV have the ability to delay host immune system clearance of the virus by integrating the DNA, modifying tissue viscoelasticity, and modulating the PI3K/AKT signaling pathway, which promotes metabolism, proliferation, cell survival, growth and angiogenesis in response to extracellular signals, *via* the HBV X protein, thus leading to oncogenesis[87].

It has been shown that fungal microbiota including *Candida*, *Saccharomyces*, *Aspergillus* or *Malassezia* spp. are involved in pancreatic oncogenesis. One proposed mechanism is that ligation of mannose-binding lectin, which binds to glycans of the fungal wall may lead to activation of the complement cascade and oncogenic progression[88].

Short-chain fatty acids (SCFA) which are metabolites from the gut microbiota and cathelicidin-related antimicrobial peptides secreted by normal pancreatic β-cells protect against tissue inflammation and control pancreatic bacterial overgrowth[89,90]. It has been shown that patients with PC have an abundance of a higher abundance of lipopolysaccharide-producing bacteria, and a reduction in beneficial microbes, such as butyrate-producing bacteria[91]. Butyrate, which is a SCFA produced by certain bacteria of gut possesses anti-inflammatory and anti-neoplastic properties in regard to PC by the means of "pro-differentiation, anti-proliferation, anti-invasion, pro-apoptosis" and chemo-sensitization effects[91]. Another SCFA from the gastrointestinal (GI) microbiota, acetate, induces insulin secretion *via* the microbiome-brain β-cell axis controlling pancreatic bacterial overgrowth[92,93]. Tryptophan metabolism can serve as an immunomodulatory factor by overexpression of indoleamine2,3-dioxygenase1 which inhibits the maturation of CD11c and dendritic cells, and T-cell proliferation and by high expression of Kyn which leads to induction and activation of the aryl hydrocarbon receptor, leading to upregulation of programmed cell death protein 1 expression; enhancing the efficacy of antitumor adoptive T-cell therapy and reducing the rate of migration and invasion in both tumor-bearing mice and patients with PC[94-96].

IMPACT OF GUT MICROBIOME ALTERATION ON THE TREATMENT OF PC

PAC is only resectable in approximately 15% to 20% of cases at the time of diagnosis, however, surgical resection offers the only chance of cure. PAC carries a dismal prognosis even after surgical resection with negative margins given its high rate of recurrence. Therefore, systemic chemotherapy, radiation therapy, and combined approaches (chemoradiotherapy) have been used both prior to and following

surgical resection in an effort to improve cure rates[97]. More recently, immunotherapy and CAR T-cell therapy have gained favor for use in the treatment of PAC[13]. The gut microbiome has been shown to interact with those treatment modalities and affect their efficacy[13,42]. Furthermore, the gut microbiome has also shown some cytotoxic effect in PAC[42].

E. coli and *Staphylococcus aureus* strains have the potential to produce Cytolysin A (ClyA), which is a pore-forming cytotoxin that possesses anticancer properties[98]. ClyA exerts its cytotoxicity, by creating multimeric pores and imposing cell death in the eukaryotic membrane by the caspase-dependent pathway[99]. *E. coli*, *A. actinomycetemcomitans*, Campylobacter and Helicobacter are known to produce Cytolethal distending toxin (CDT)[100]. CDT is known to have genotoxic attributes by DNase activity which creates DNA double stranded breaks, leading to cell cycle arrest and cytotoxicity[49]. Streptococcus pyogenes secretes streptolysin O which is implicated in cytolysis and apoptosis[101].

Prebiotics are defined as nutrients that are degraded by gut microbiota and may affect not only the intestinal microenvironment but also distant organs. In a mice study by Trivieri *et al*[102] using xenograft mice model confronted with PC gene expression dataset (GSE16515) and investigating the impact of high levels of prebiotic resistant starch diet (RSD) on miRNA expression profiles in tumor tissues, RSD was associated with dysregulation of 19 miRNAs genes expression in comparison to control. subsequent analysis revealed that part of genes participating in the regulation of processes such as the development of carcinoma, inflammatory response, abdominal cancer, metabolic disease, growth, invasion, and metastasis were downregulated in a group of mice fed with RSD in comparison to control. Furthermore, genes participating in the synthesis of carbohydrates, glucose metabolism disorder, and cell death of cancer cell lines were significantly upregulated in mice fed with RSD. Thus, the authors concluded that there is prolonged overall survival and beneficial value of RSD in PAC[103].

Lactobacillus casei is a probiotic that can produce Ferrichrome, which has the potential to suppress the growth of refractory PC cells by inhibiting cancer cells progression and dysregulating cell cycle by activating P53[102,103]. Next-generation probiotics such as *Akkermansia muciniphila* (*A. muciniphila*), are identified using next-generation sequencing and bioinformatics tools. *A. muciniphila* has been shown to inhibit the proliferative activity of INS-1 (rat pancreatic islet cell tumor cells) in a mouse model[104].

FOLFIRINOX, which is a commonly used regimen in PAC is composed of leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin. Oxaliplatin has an immunomodulatory effect as well, potentiating tumoricidal T-cell immunity. In a mice model, a group with a defective TLR signaling pathway, demonstrated no response to oxaliplatin treatment[105]. Agonistic TLR molecules from microbial membranes were reported to help stimulate the immune system and increase reactive oxygen species production, thus enhancing the tumoricidal activity of oxaliplatin[105]. Irinotecan is characterized by common GI side effects limiting the dose and effectiveness of treatment. Those side effects can be modulated by enzymatic activity of the gut microbiome, with some bacteria improving the side effects profile, while others may worsen the side effects. The β-glucuronidase enzyme produced by intestinal bacteria cleaves the active irinotecan metabolite SN-38G into a toxic form that damages the colonic mucosa and causes GI side effects. The literature revealed that antibiotics or modification of gut microbiomes significantly alleviated the GI toxicity in cancer patients[106]. Furthermore, reduced risk of developing irinotecan toxicity has been shown with the use of indigestible fibers, using appropriate probiotics and adequate butyrate intake[107].

Several animal studies showed that mice housed in germ-free conditions and animals treated with broad-spectrum antibiotics showed reduced effects of immunotherapy by a combination of TLR-9 antagonist and anti-interleukin-10 antibody. Furthermore, the ineffectiveness of cancer immunotherapy directed against the major negative regulator of T cell activation cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) was observed when applied to antibiotic-treated animals or germ-free mice[108]. Monoclonal antibodies that neutralize CTLA-4 have been shown to rely on the intestinal microbiota, in particular, Bacteroidales and Burkholderiales[108]. A recent study used a gut microbe-derived metabolite trimethylamine N-oxide (TMAO) that showed enhanced anti-tumor immunity to PAC. TMAO was delivered either intraperitoneally or *via* a dietary choline supplement to orthotopic PAC bearing mice, and lead to reduced tumor growth and associated with an immunostimulatory tumor-associated macrophage phenotype and activated effector T cell response in the tumor microenvironment. The combination of TMAO and immune checkpoint inhibitors (ICI) such as programmed cell death 1, in a mouse model of PAC, proved to be superior in reducing tumor burden and improving survival compared to either therapy alone[109].

CAR T-cell therapy has shown tremendous results in hematologic malignancies. Only recently, it was tried on non-hematologic malignancies with promising preliminary data. CAR T-cell therapy of solid tumors faces a major issue in that commonly targeted tumor antigens are expressed at low levels in normal tissues, leading to on-target off-tumor toxicity. CEACAM7, which has low to undetectable expression in all normal tissues and with strong surface expression on a subset of primary human PAC tumors was identified as a potential target antigen for CAR T-cell therapy of PAC. CAR T-cells targeting CEACAM7 were generated in a study by Raj *et al*[13] and showed significant antitumor activity against patient-derived PAC tumor cultures both *in vitro* and *in vivo*[13]. A brief summary can be found in Table 2.

Oncolytic adenoviruses have been engineered to replicate in cancer cells and controlling tumor progression. Oncolytic adenovirus AdNuPARmE1A with miR-222 binding sites, are made to withdraw

Table 2 Impact of gut microbiota in the treatment of Pancreatic cancer

Bacteria	Primary site	Potential mechanism	Subsequent effect	Ref.
Escherichia coli	Large bowel	Cytolysin A production; Cytolethal distending toxin production	Imposing cell death in the eukaryotic membrane by the caspase-dependent pathway; DNA double stranded breaks, leading to cell cycle arrest and cytotoxicity	[49, 86,87]
Staphylococcus aureus	Variable	Cytolysin A production	Imposing cell death in the eukaryotic membrane by the caspase-dependent pathway	[86]
Streptococcus pyogenes	Variable	Streptolysin O production	Increase in apoptosis and cytolysis	[88]
Aggregatibacter actinomycetem-comitans, Campylobacter and Helico-bacter	Mouth, stomach, large bowel	Cytolethal distending toxin production	DNA double stranded breaks, leading to cell cycle arrest and cytotoxicity	[87]
Lactobacillus casei	Mouth and small intestine	P53 activation	Upregulation of apoptosis	[90]
Bacteroidales, Burkholderiales	Large bowel	CTLA-4 upregulation	Enhancing activity of monoclonal antibody against CTLA-4	[95]

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4.

the miRNA from the cellular environment. AdNuPAR-E-miR222-S mediated-decrease of miR-222 expression in pancreatic cancer cells was shown to strongly improve the viral yield and enhance the adenoviral cytotoxic effects[110].

INTRATUMORAL MICROBIOME IN PANCREATIC CA

Intratumoral microbiome is derived from 3 basic mechanisms; (1) Sloughing of the mucosal barrier; (2) Adjacent normal tissues; and (3) Hematogenous spread[111]. Interestingly, Nejman *et al*[112] demonstrated that amongst the tumors that they studied, every tumor was associated with a completely different microbiome composition[112]. The pancreas is traditionally thought to be a 'bacteria-free' organ. However, bacterial DNA belonging to the Proteobacteria phylum was very abundantly found in pancreatic cancer[112]. Another study which confirmed increased amounts of bacterial DNA in pancreatic cancer *vs* normal pancreatic tissue was the study by Geller *et al*[113]. Bacterial ribosomal DNA was detected *via* FISH technique in 76% of patients with PAC *vs* 15% of patients with normal pancreatic tissue[88]. Similarly, by using the FISH technique, Aykut *et al*[88] demonstrated that *Pseudomonadota*, *Bacillota*, and *Bacteroides* were the most abundant bacteria found intratumorally in pancreatic cancer patients[88]. Interestingly, the fungal mycobiome in pancreatic tissue samples obtained from patients with PAC was also found to be very distinct from healthy individuals with a high prevalence of Malassezia[88].

MICROBIOME IMBALANCE AND PANCREATIC CA

Dysbiosis or imbalance in the microbiome has been shown to impact the inflammatory cascade in a non-physiological way and in turn, contribute to the development of cancer[114]. The known risk factors for pancreatic carcinoma are smoking, advancing age, type 2 diabetes mellitus, chronic pancreatitis, and obesity. Interestingly, many of these risk factors have been recently found to be associated with an imbalance in the microbiome, which may increase the risk of PAC[115-118]. A meta-analysis by Maisonnuevve demonstrated a positive correlation between periodontal disease and PAC[119]. This may be related to an imbalance in the oral microbiome. Oral microbiomes have been shown to be associated with carcinogenesis *via* inducing systemic inflammation, and the most important being Porphyromonas Gingivalis[120-122]. A case control study demonstrated that the risk of PAC was 2-fold higher in patients with a higher level of antibodies against a specific strain of *P. Gingivalis*, whereas higher levels of antibodies against commensal oral microbiome were actually protective against PAC, with an almost 50% lower risk of the cancer in patients who had these antibodies[123]. In-vivo studies have shown that *P. gingivalis* enhances the proliferation of pancreatic tumor cells, regardless of the concentration of TLR-4. Furthermore, the concentration and proliferation of *P. gingivalis* is greatly increased in PAC tissue secondary to hypoxia, which is very prevalent in the cancer microenvironment[124]. Furthermore, bacteria that cause periodontitis are also found to cause K-ras and p53 mutations, and those have in turn been associated with poor prognosis in patients with pancreatic cancer[125]. They also demonstrated that the number of cases of pancreatic cancer were higher in patients who had GI infections from *H.*

Pylori, Enterobacter, and Enterococcus species[125].

This prior literature leads us into sensibly concluding that possibly, an imbalance in the oral microbiome is associated with an increased risk of PAC, however, reverse causation is an important factor that needs to be excluded before exploring this aspect further. One study evaluated this and found that 2 oral bacteria-*P. gingivalis* and Aggregatibacter actinomycetemcomitans are associated with an increased risk whereas *Leptotrichia* genus of *Fusobacterium* species was associated with a reduced risk of PAC. Interestingly, even after excluding patients who developed the cancer within 2 years from the date of sample collection, the risks remained elevated[10]. This significantly reduces the likelihood of reverse causation. Another significant study going in favor of a causality between *E. faecalis*, and pancreatic cancer is the one by Maekawa *et al*[126], wherein the level of antibodies against *E. faecalis* capsular polysaccharide were found to be increased in the serum of pancreatic cancer patients[126]. However, larger cohort studies are needed on the subject to conclusively establish causation.

CONCLUSION

Despite advances in medicine and the discovery of newer anticancer therapies, the prognosis of pancreatic cancer remains dismal. By the way of this review, we found that a prebiotic resistant starch diet has been associated with better overall survival in PAC. We also found that periodontal diseases increase the risk of developing PAC. This is especially important as periodontal diseases should be avoided and promptly treated in patients with a family history of PAC, other risk factors for PAC, and those with known/suspected genetic mutations susceptible for the development of PAC. Furthermore, we found that the use of concomitant antibiotics can positively or negatively affect treatment of PAC. Some gut microbiomes can enhance the effect of therapy and improve tolerance to therapy as well. Thus, neutropenic diet can be avoided in select patients meeting the requirements. Newer therapeutics such as ICI and CAR T-cell therapies can play a major role in the outcome of PAC, however, most promising studies are done in animal models. We hope that in the near future, there will be more clinical trials in human subjects replicating the promising results from animal studies which will possibly offer newer ways to handle this very deadly malignancy.

FOOTNOTES

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