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SYSTEMATIC REVIEWS

Microbiome and pancreatic cancer: A comprehensive topic review of literature

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Abstract

AIM

To review microbiome alterations associated with pancreatic cancer, its potential utility in diagnostics, risk assessment, and influence on disease outcomes.

METHODS

A comprehensive literature review was conducted by all-inclusive topic review from PubMed, MEDLINE, and Web of Science. The last search was performed in October 2016.

RESULTS

Diverse microbiome alterations exist among several body sites including oral, gut, and pancreatic tissue, in patients with pancreatic cancer compared to healthy populations.

CONCLUSION

Pilot study successes in non-invasive screening strategies warrant further investigation for future translational application in early diagnostics and to learn modifiable risk factors relevant to disease prevention. Pre-clinical investigations exist in other tumor types that suggest microbiome manipulation provides opportunity to favorably transform cancer response to existing treatment protocols and improve survival.

Key words: Pancreatic Cancer; Human microbiome; Biomarkers, cancer; Cancer screening tests; Treatment effectiveness

Core tip: Recent literature reports influences of microbiome alterations contributing to carcinogenesis of pancreatic cancer. The poor prognostics of pancreatic cancer are related to late recognition and treatment resistance, thus warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect outcomes. Learning the role of microbiome in carcinogenesis may lead to identifying reliable, non-invasive screening strategies, and additional modifiable risk factors. Microbiome studies in pancreatic cancer could offer therapeutic targets and an extraordinary opportunity to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

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INTRODUCTION

A commensal microbiome, by definition maintains a symbiotic relationship in healthy individuals, offering protection from disease by nutritive, inflammatory-modulating activity, hormonal homeostasis, detoxification, and metabolic effects of bacterial metabolites[1-3]. Dysbiosis is the manifestation of a corrupt, imbalanced microbiome, which contributes to pathogenesis of several diseased states[2]. Recently, there are literature reports on influences of microbiome alteration contributing to carcinogenesis of multiple malignancies[1,2,4-6]. A classic pathogen in the literature is *Helicobacter pylori* (*H. pylori*), which has revealed inconsistent and paradoxical associations pending the body site studied[7,8]. *H. pylori* has been extensively scrutinized as a risk factor for development of pancreatic cancer and an association is controversial[9-12]. Pancreatic cancer often denotes a poor clinical prognosis in part due to late recognition and treatment resistance, warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect outcomes[13,14].

MATERIALS AND METHODS

Search methods: PubMed, MEDLINE, and Web of Science for medical search terms: "pancreatic cancer" and "microbiome," "carcinogenesis," antibiotic," "probiotic," "microorganism," "bacteria," "colonization," "cachexia," or "infection." The relevant articles reference lists were also searched manually for additional articles. The last search was performed in October 2016.

Selection criteria: Manuscripts and abstracts describing pre-clinical studies, animal models, epidemiological studies, case series, case-control, retrospective chart reviews, prospective studies, pilot, meta-analysis, and literature topic reviews were included. There were no randomized clinical trials identified from these search terms. Articles were limited to abstract and manuscript publications in the English written language.

RESULTS

Characterization of the healthy microbiome spectrum is ongoing. In 2012, the NIH Human Microbiome Project[3], demonstrated no microbial taxa were universally present across all humans in a single body site. The oral cavity contains an extensive reservoir of bacteria with more than 700 species observed, most of which have not been cultured in a laboratory[15,16]. Healthy oral habitats are dominated by Streptococcus, followed by Haemophilus in the buccal mucosa, Actinomyces in the supragingival plaque, and Prevotella in adjacent, low-oxygen subgingival region[3].

Oral microbiome and pancreatic cancer

Alterations in the ecological balance of the microbiome exist during diseased oral cavity states including gingivitis and periodontal disease compared to a healthy oral cavity[16-20]. Periodontal disease, manifested by an inflamed oral activity, pathogenic oral flora, and tooth loss are well-established independent risk factors associated with development of pancreatic cancer[21-23]. Therefore, the shifts in taxa dominance and diversity of bacterial communities that deviate from an established healthy microbiome may be reflective of disease states[2,3]. Pilot studies have proposed a role in oral pathogenic bacteria in periodontal disease as an early screening test and as a biomarker of pancreatic cancer[12,24,25]. Several dedicated studies have aimed to define microbiome changes in the oral cavity associated with pancreatic cancer, results are summarized in Table 1.

Oral microbiome and pancreatic cancer summary

Oral flora alterations exist in pancreatic cancer patients compared to healthy populations. Salivary RNA studies reveal *bacteroides* genus and *Granulicatella adiacens* are more common in pancreatic cancer patients than healthy subjects[12,24]. However, *Neisseria elongata*, *Streptococcus mitis*, *Corynebacterium* genus, and the *Aggregatibacter* genus are present in lower concentrations in pancreatic cancer than

Table 1 Oral microbiome and pancreatic cancer

Ref.	Study design	Case No.	Control No.	Detection Method	Bacteria association	Outcome	Author conclusion
Michaud *et al*[18], 2013, Western Europe	Prospective	405	416	Plasma IgG	*Porphyromonas gingivalis* ATTC 53978	High titer *P. gingivalis* (IgG > 200 ng/mL) OR 2.14 $P = 0.05$	Two fold increase in pancreatic cancer among individuals with high titer *P. gingivalis*
					High titer, *commensal* bacteria	OR = 0.55 95%CI: 0.36-0.83	45% lower risk of pancreatic cancer compared to individuals with lower antibody levels
Farrell *et al*[12], 2012, United States	Case-control	28	28	Salivary qPCR, Microarray	*Neisseria elongata* and *Streptococcus mitis*	*N. elongata* and *S. mitis* significantly decreased ROC-plot AUC 0.90; 95%CI: 0.78-0.96, $P < 0.0001$	*N. elongate* and *S. mitis* combination ROC plot AUC 0.90 serves as 96% sensitive, 82% specific biomarker for pancreatic ca *vs*. healthy subjects
					Granulicatella adiacens	*G. adiacens* Significantly elevated compared to healthy control	
Lin *et al*[24], 2013, United States	Pilot	13	12	Salivary rRNA	*Bacteroides genus*	More common pancreatic cancer patient *vs* healthy subjects $P = 0.002$	Oral flora alterations in microbiome in pancreatic cancer exist compared to healthy individuals
					Corynebacterium genus *Aggregatibacter* genus	Less common in pancreatic cancer *vs* healthy subjects $P = 0.033$ and 0.019	
Torres *et al*[25], 2015 United States	Cross-sectional	8	22	Salivary rRNA, PCR	Higher *Leptotrichia* and lower *Porphyromonas* colonization	*Lepotrichia:Porphyromonas* ratio elevated in pancreatic cancer *vs* healthy control $P = 0.001$	L:P ratio may be reliable biomarker for pancreatic cancer diagnosis
Fan *et al*[26], 2016 United States	Nested Case control	361	371	Salivary rRNA gene sequencing	Oral pathogens *P. gingivalis*, *A. actinomycetemcomitans*	*P. gingivalis* AOR = 1.60 (95%CI: 1.15-2.22) *A. actinomycetes* OR = 2.20 (95%CI: 1.16-4.18)	Presence of oral pathogens are related to subsequent increased risk of pancreatic cancer. On contrary, *Fusobacteria* and *Leptotrichia* are associated with dose or concentration dependent decrease risk of pancreatic cancer
					Fusobacteria and *Leptotrichia*	*Fusobacteria* decreased risk OR per percent increase of relative Abundance OR = 0.94 (95%CI: 0.89-0.99) *Lepotrichia* OR = 0.87 (95%CI: 0.79-0.95)	

healthy subjects[12,24]. Combining salivary RNA biomarkers for *N. elongata* and *S. mitis* yielded an ROC-plot AUC value of 0.90 with 96.4% sensitivity and 82.1% specificity in distinguishing patients with pancreatic cancer from healthy subjects[12]. A cross-sectional study[25] identified of a significantly higher *Leptotrichia* and lower *Porphyromonas* colonization in pancreatic cancer patient saliva, translating to an *Leptotrichia:Porphyromonas* (L:P) ratio of biomarker significance. In this same study, a patient classified with an unknown digestive disease presented with an elevated L:P ratio that led to dedicated workup revealing a new diagnosis of pancreatic cancer[25]. Pilot successes deserve further exploration into utilizing salivary markers as potentially valuable non-invasive, economical screening strategies.

Interestingly, the highest concentration of plasma antibodies *to Porphyromonas gingivalis* (strain ATTC 53978), a pathogenic bacteria associated with periodontal disease, was linked with a 2-fold increased risk of pancreatic cancer[18]. The association was amplified over time, with the addition of 5 or 7 year lag[18]. Similar to case control studies of saliva samples revealing oral pathogens, *P. gingivalis* and *A. actinomycetemcomitans* are associated with increased risk for subsequent development of pancreatic cancer[26]. This finding is consistent with epidemiologic data that periodontal disease is an independent risk factor for pancreatic cancer development[20,23,27]. Alternatively, high antibody titers against non-pathogenic, commensal bacteria were associated with 45% decreased risk of pancreatic cancer compared to those with a lower antibody level profile[18]. Similarly *Fusobacterium* and *Lepotrichia* are protective and decreases risk, also in a dose dependent relationship[26]. *Lactobacillus* is a commensal oral cavity bacterium that diminishes gingival inflammation and cariogenic periodontal pathogenic bacteria[28]. Thus, with the clearly established role of periodontal disease and associated periodontal pathogens for pancreatic cancer risk profiles, any measures to prevent periodontal pathogens may serve protective role to prevent pancreatic cancer, but has not been studied on this topic specifically.

H. pylori and pancreatic cancer

There is literature that illustrates a paradoxical nature of microorganisms relative to by site and tumor studied. For example, eradication of *H. pylori* causes regression of MALT lymphoma and decreases risk of metachronous gastric carcinoma after endoscopic resection for early stage gastric cancer[1,29]. However, *H. pylori* gastric colonization decreases the risk of oesophageal adenocarcinoma that does not involve the gastric cardia[30]. *H. pylori* is a diverse bacteria with several virulent strain variations. Among the best studied are *Cytotoxin-associated gene A* (*Cag-A*) positive strains that express Cag-A virulence factor, which is linked to gastric inflammation, ulceration, and promoting malignant transformation in gastric cancer[31,32]. *H. pylori* and *Cag-A* dominate microbiome studies in pancreatic cancer. Study results are variable and complex, as is noted in Table 2[9-11,33-42].

H. pylori and pancreatic cancer summary

Results from *H. pylori* case studies in pancreatic cancer reveals complex mixed results pending virulence strain *cag-A* status. Consensus from recent meta-analysis is that there is a modestly significant increased risk associated with development of pancreatic cancer for *cag-A*-negative *H. pylori* strain[9-11,39], with positive correlated adjustment factors including non-O blood type[37,43] and active smoking status[34,36]. The general literature trend summarized in Table 2 is *cag-A*-positive strains results in decreased risk or non-significant association with pancreatic cancer. Notable global population differences exist as the majority of studies highlighted in this review are mainly relevant to Western European or North American ethnic groups. The results of one meta-analysis addressing global studies[41] and pancreatic cancer risk including two Eastern Asian population case-cohorts that suggest a decreased risk of pancreatic cancer risk for *H. pylori* seropositivity overall, including *Cag-A*-positive strains in Eastern Asian ethnic region[41].

Tissue microbiome and pancreatic cancer

We found three human pancreatic adenocarcinoma tissue studies dedicated to microbiome alterations or their effect on the tumor microenvironment (Table 3[44-46]).

Tissue microbiome and pancreatic cancer summary

In one case control study, enteric strains of *Helicobacter* DNA were demonstrated to colonize the pancreas in 75% of adenocarcinoma patients but not in pancreatic controls with benign disease[44]. Among proposed mechanisms for dissemination may result from hepatobiliary translocation or hematogenous seeding[44,46]. However, DNA of different *Helicobacter* species is mutually exclusive by sampled site[44]. For example, *Helicobacter* identified in the pancreas compared with *Helicobacter* of gastroduodenal tissue of the same patient were different *Helicobacter* subspecies[44]. Thus, dissemination of *H. pylori* from the stomach to the pancreas is unlikely, instead a subspecies tissue tropism may exist[44].

Both direct microbe colonization and downstream proliferative metabolic affects may promote tumor-associated inflammation preserved by low-grade chronic inflammation[6,29,47] . Evidence of this effect in a pre-clinical study of human a pancreatic cell line showed *H. pylori* colonization of a human pancreatic cell line expressed increased factors for malignant potential including proliferative factors, NF-kappa-B, activator protein-1, proflammatory IL-8 activity, vascular endothelial growth factor secretion, and the growth factor promoter, serum response element[45]. The overall result is activation of molecular pathways for tumor growth and progression in the setting of *H. pylori* infection[45].

Fusobacterium is an anaerobic, oral bacterium that has been identified in pancreatic abscesses and carries unfavorable prognostic implications in some gastrointestinal cancers[46]. To explore a role for *Fusobacterium* in pancreatic cancer, surgical specimens of pancreatic adenocarcinoma were analyzed for presence of this bacterium. Only 8% of specimens in this cohort contained *Fusobacterium* colonization[46]. However, pancreatic ductal adenocarcinoma surgical specimens with presence of *Fusobacterium* colonization was identified as an independent predictive factor for shorter survival compared to *Fusobacterium* negative tumors[46]. The *fusobacterium* positive sample group also demonstrated 28% detection of paired normal tissue[46]. The presence of *Fusobacterium* in normal tissue margin suggests it may contribute to malignant potential, but this theory requires further exploration[46].

DISCUSSION

The oral microbiome has a protective role against pancreatic cancer in a healthy, commensal state, but may promote malignancy in a pathologic state[1,2,4-6,12,18,24,25]. Shifts in taxa dominance and diversity of oral bacterial communities, especially those reflective of periodontal disease are associated with increased pancreatic cancer risk[12,18,24,25]. This correlates clinically with periodontal disease status, a validated independent risk factor for development of pancreatic cancer[21-23]. Bacterial markers of periodontal disease[18] and shifts in microbial taxa diversity[12,24,25] have promising potential to serve as non-invasive screening biomarkers of pancreatic cancer. The evidence is strong enough to

Table 2 ***Helicobacter pylori*** **and pancreatic cancer**

Ref.	Study Design	Case No.	Control No.	Detection Method	Bacteria association	Outcome	Author conclusion
Raderer *et al*[33], 1998, Austria	Case-control	92	27	Plasma IgG ELISA	*H. pylori*	OR = 2.1 95%CI: 1.1-4.1 P = 0.035	*H. pylori* seropositivity prominent in pancreatic cancer patients compared with colorectal cancer combined with normal controls
Stolzenberg-Solomon *et al*[34] 2001, Finland	Nested case-control	121	226	Plasma IgG ELISA	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* OR = 1.87; 95%CI: 1.05-3.34 CagA+ strains OR = 2.01; 95%CI: 1.09-3.70	Male smokers seropositive for *H. pylori* were nearly twice as likely to develop pancreatic cancer compared to seronegative. Stronger influence adjusting for years of smoking
de Martel *et al*[35], 2008, United States	Nested Case-control	104	262	Plasma IgG ELISA	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* OR = 0.85; 95%CI: 0.49-1.48 CagA+ OR = 0.96; 95%CI: 0.48-1.92	*H. pylori* infection is not associated with development of pancreatic cancer
Lindkvist *et al*[36], 2008, Sweden	Nested Case-control	87	263	Plasma IgG ELISA	*H. pylori*	*H. pylori* overall OR = 1.25 95%CI: 0.75-2.09 *H. pylori* in Never smokers AOR = 3.81 95%CI: 1.06-13.63	Adjusted risk for development of pancreatic cancer highly increased in never-smokers seropositive for *H. pylori*
Risch *et al*[37] 2010, United States	Case-control	373	690	Plasma IgG ELISA	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	CagA negative *H. pylori* non-O blood group OR = 2.78, 95%CI: 1.49-5.20, P = 0.0014; CagA negative *H. pylori* O-blood group OR = 1.28, 95%CI: 0.62-2.64, P = 0.51	CagA-negative *H. pylori* seropositivity is a risk factor for pancreatic cancer among individuals with non–O blood type
Trikudanathan *et al*[11], 2011	Meta-analysis	822	1513	meta-analysis of 6 case control studies	*H. pylori*	AOR = 1.38, 95%CI: 1.08-1.75	Significant positive association between the presence of *H. pylori* infection and pancreatic cancer.
Gawin *et al*[38], 2012, Poland	Case-control	139	177	Plasma IGg, ELISA, western blot	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* OR = 1.27; 95%CI: 0.64-2.61 P = 0.514 CagA+ OR = 0.90; 95%CI: 0.46-1.73, P = 0.744	No association between seropositivity of *H. pylori* or CagA with development of pancreatic cancer
Xiao *et al*[39], 2013	Meta-analysis	1083	1950	meta-analysis of 9 case-control studies	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* Overall OR = 1.47 95%CI: 1.22-1.77 Adjusted for "High quality" studies AOR = 1.28; 95%CI: 1.01-1.63 Adjusted for CagA positive AOR = 1.47; 95%CI: 0.79-2.57	Borderline positive association *H. pylori* seropositivity overall. Adjusted risk for high quality studies revealed a significant, but modest association. CagA virulence seropositivity was not associated with pancreatic cancer
Yu *et al*[40], 2013, Finland	Case-control	353	353	multiplex serology to 4 *H. pylori* antigens	*H. pylori*	OR = 0.85; 95%CI: 0.49 -1.49	No association between seropositivity of *H. pylori* with development of pancreatic cancer

Wang *et al*[41], 2014	Meta-analysis	2049	2861	Meta-analysis of 9 case-control studies (2 non- English language)	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* overall OR = 1.06, 95%CI: 0.74-1.37 Eastern Asian Population *H. pylori* OR = 0.62, 95%CI: 0.49-0.76 Cag-A positive OR = 0.66, 95%CI: 0.52-0.80 Western European population *H. pylori* OR = 1.14 95%CI: 0.89-1.40 Cag-A positive OR = 0.84 95%CI: 0.63-1.04	Eastern Asian populations demonstrate significant decreased risk pancreatic cancer associated with *H. pylori* seropositivity. No association present in Western populations
Risch *et al*[42], 2014, Shanghai	Case-control	761	794	Plasma IGg, ELISA	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	Cag-A positive *H. pylori* AOR = 0.68; 95%CI: 0.54-0.84 Cag-A negative *H. pylori* AOR = 1.28; 95%CI: 0.76-2.13	Decreased pancreas-cancer risk was seen for CagA positive *H. pylori* compared to seronegativity for both *H. pylori* and CagA. A modest increased risk for CagA-negative *H. pylori* seropositivity
Chen *et al*[9], 2015	Meta-analysis	1446	2236	meta-analysis of 5 case control studies	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	Overall OR = 0.99; 95%CI: 0.65-1.50 CagA+ OR = 0.92; 95%CI: 0.65 -1.3 Virulent strain infection OR = 0.97 95%CI: 0.50-1.89 Nonvirulent infection OR = 1.47 95%CI: 1.11-1.96	CagA-negative, nonvirulent strains of *H. pylori* may be a risk factor for pancreatic cancer. No association with seropositivity for *H. pylori* infection overall, nor when adjusted for CagA or virulent strain infection
Schulte *et al*[10], 2015	Combination Case-control and meta-analysis	580	626	Plasma IGg, ELISA and meta-analysis of 10 case-control studies	cytotoxin-associated gene-A (CagA) virulence factor and *H. pylori*	*H. pylori* overall OR = 1.00 95%CI: 0.74-1.35 Cag-A negative AOR = 1.23 95%CI: 0.83-1.82 Cag-A positive OR = 0.74 95%CI: 0.48-1.15	No overall association observed for *H. pylori* seropositivity and risk of pancreatic cancer, but evidence of non-significant CagA strain-specific associations

warrant targeted risk reduction strategies in patient education and modifiable lifestyle counseling regarding maintenance of oral hygiene.

A directly carcinogenic role for *H. pylori* has been explored after discovering enteric strains of *Helicobacter* DNA demonstrated to colonize the pancreas in a majority of sampled pancreatic adenocarcinoma but not in patients with benign disease[44]. A preclinical study[45] examined direct *H. pylori* colonization and associated activation of molecular pathways for tumor growth and progression[45]. These downstream molecular effects highlight oncogenic potential with microbiome influence that promotes tumor-associated inflammation preserved by low-grade chronic inflammation[6,29,47]. Despite the existence of several proposed carcinogenic mechanisms of dysbiosis, inflammation is a central facilitator illustrated in pancreatic cancer murine models, human cell lines, and tumor translational expression profiles[6].

Future directions

There have been studies that indicate the microbiome and antibiotics modulate tumor response to chemotherapy[48,49]. Germ-free and antibiotic treated murine models highlight the protective effect of commensal bacteria by shaping the inflammatory network required for favorable response to anti-tumor therapy[48]. In murine models, platinum therapy eliminated most subcutaneous lymphoma tumors and prolonged survival in control mice[48]. However, antibiotic-treated and germ free mice failed to respond to platinum-treatment, in part by decreasing reactive oxygen species[48]. Similarly, CTLA-4 inhibitor treated murine models with sarcoma suggest that gut microbiota, specifically *bacteroides* subspecies, are required for the successful anti-tumor effects

Table 3 Tissue microbiome and pancreatic cancer

Ref.	Study design	Case sample size	Detection method and sample	Bacteria association	Outcome	Author conclusion
Nilsson *et al*[44], 2006, Sweden	Case-control	84	DNA genus specific PCR, surgical specimen	*H. pylori*	*Helicobacter* DNA detected in pancreas of 75% patients with adenocarcinoma, but not detected in any control	*Helicobacter* DNA, mostly *H. pylori* genus, commonly detected in pancreatic cancer
Takayama *et al*[45], 2007, Japan	Abstract	-	ELISA and western blot, Pre-clinical cell line	*H. pylori*	IL-8 and VEGF secretion and proliferation factors NF-kappa-B, AP-1, and serum response element of human pancreatic cells increased by *H. pylori* infection	*H. pylori* infection of human pancreatic cells may increase malignant potential of pancreatic cells
Mitsuhashi *et al*[46], 2015, Japan	Case-control	283	PCR, surgical specimen	Fusobacterium	Detected in 8.8% cases. Median cancer-survival (mo) positive *vs* negative detection 17.2 *vs* 32.5 for log-rank $P = 0.021$	significantly shorter survival observed in the *Fusobacterium* species-positive group

of CTLA-4 blockade[49]. Notably, antibiotic and germ free mice with sarcomas do not respond to CTLA-4 inhibitor at baseline, but recover antitumor activity with recolonization of gut commensals by human fecal microbiota transplantation of specific *bacteroides* subspecies[49]. Oral administration of *Bifidobacterium* in murine models with melanoma augments the immune response to tumor cells, in part by dendritic cell activation of the innate immune system[49]. This effect was not observed with administration of *lactobacillus* species, suggesting a complex, species specific modulation of the immune system *in vivo*[49]. The potential to utilize probiotics in humans to amplify antitumor response to existing chemotherapy and immunotherapy protocols requires further investigation[50].

Anti-tumor therapy and commensal flora collaborate in part, by loss of TNF-dependent early tumor necrosis response, down-regulation of inflammatory cytokines, phagocytosis, antigen presentation, and adaptive immune response gene expression controlling tissue development and cancer[48]. The loss of commensal organisms by antibiotics and the possibility of carcinogenic promoting effects of antibiotics have been explored. The risk related to pancreatic cancer seems limited to the penicillin class, especially with more than five courses, but this risk diminishes over time[51]. Macrolides, cephalosporins, tetracyclines, antivirals, and antifungals were not associated with increased risk of pancreatic cancer[51]. The impact of antibiotics on commensal framework may explain the need for repeated antibiotic exposures, leading to an enduring change in bacterial community diversity[51]. Murine models demonstrate *lactobacillus* was among quickest flora to recover in the gut after antibiotic therapy. However, the effect of antibiotics on the gut microbiome is enduring at four weeks after exposure; the population is deficient, and not reflective of its healthy, baseline, pre-antibiotic diversity[48].

Commensal bacteria offer protection from disease by inflammatory-modulating activity as above, but also by hormonal homeostasis, detoxification, and metabolic effects of bacterial metabolites. For example, murine models show *lactobacilli* are consistently reduced in cachectic mouse models[52]. A *lactobacilli* cocktail combination with prebiotic substrate that supports growth of microorganisms, changes the dysbiotic populations of cecal microbiota composition in murine models, clinically resulting in improved survival and reduction of cachexia[53]. These are highly important implications in pancreatic adenocarcinoma population since these patients carry the strongest burden of cancer cachexia among all malignancies, present in up to 80% of patients[54,55] resulting in reduced survival and progressive disease[55-57]. Weight stabilization alone significantly proven to improve survival in pancreatic adenocarcinoma patients with unresectable disease[58].

In conclusion, the initial motive to explore microbiome role in carcinogenesis may lead to identifying reliable non-invasive screening strategies and discern additional modifiable risk factors. With further investigation, potentially microbiome studies in pancreatic cancer could offer therapeutic targets. Perhaps the most extraordinary opportunity is to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

COMMENTS

Background

Recently, there are literature reports on influences of microbiome alteration contributing to carcinogenesis of multiple malignancies. Among the most controversial is dysbiosis related to pancreatic cancer. Pancreatic cancer often denotes a poor clinical prognosis in part due to late recognition and treatment resistance, warranting investigations for modifiable risk factors, early screening biomarkers, and microenvironment elements that affect patient outcomes.

Research frontiers

Murine models demonstrate commensal microbiome taxa modulates a favorable tumor response to chemotherapy in multiple tumor types In addition, manipulation of cecal microbiome composition with lactobacillus in murine models, have resulted in improved survival and reduction of cachexia a clinically significant burden in the majority of pancreatic cancer patients.

Innovations and breakthroughs

This review article serves to update literature on microbiome alterations associated with pancreatic cancer, its potential utility as an early screening biomarker, examine the influence of the microbiome in antitumor therapy, and the potential impact of microbiome manipulation to affect pancreatic cancer patient outcomes.

Applications

Exploring the microbiome role in carcinogenesis may lead to identifying reliable non-invasive screening strategies and discern additional modifiable risk factors. With further investigation, potentially microbiome studies in pancreatic cancer could offer therapeutic targets. Perhaps the most extraordinary opportunity is to favorably transform cancer response to existing treatment protocols and improve survival by reduction of cancer-related cachexia by manipulating human gut microbiota.

Peer-review

This review describes the relationships between microbiome and pancreatic cancer. The data in this report is of considerable importance in investigations for modifiable risk factors of pancreatic cancer.

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