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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 85778

Title: Impact of gut microbiome in the development and treatment of Pancreatic cancer: newer insights.

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00004011
Position: Associate Editor
Academic degree: PhD
Professional title: Professor
Reviewer's Country/Territory: Greece
Author's Country/Territory: United States

Manuscript submission date: 2023-05-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-18 15:10

Reviewer performed review: 2023-05-18 15:13

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

it is a well written and documented manuscript.

Re: Thank you very much for recognizing the hard work put together by the authors.

It will be helpful if the authors emphasize regarding microbiome and different PC ie adenocarcinoma, IPMN etc

Re: Thank you for this observation, however, the authors specified that the term pancreatic cancer in this review referred to pancreatic adenocarcinoma (line 47-48, marked in green).

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Reviewer's code: 03252941
Position: Editorial Board
Academic degree: MD

Professional title: Doctor, Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2023-05-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-05-16 23:16

Reviewer performed review: 2023-05-23 11:30

Review time: 6 Days and 12 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Bangolo et al. performed a comprehensive review on the impact of gut microbiome in the development and treatment of pancreatic cancer (PC). Beginning with a review of the diagnosis and treatment of PC, the impact of gut microbiome on inflammation, carcinogenesis and treatment is adequately described, citing appropriate references. This is a well-written review. Especially, association between periodontitis and PC is a timely and interesting topic.

Re: Thank you very much for this keen observation and for recognizing the hard work of the authors.

While reading this manuscript, I noticed some minor points. I will list them below. 1. (Line 54) Approximately 15 percent of PCs are related to genetics: The meaning of this sentence is obscure. As described below, familial PC comprises 10% of PC patients. On the other hand, nearly all PC must have genetic aberrations in cancer-related genes including K-ras, CDKN2A, p53, and SMAD4. Please explain what this 15% means.

Re: Thank you for this great observation, as a matter of fact the sentence "Approximately

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15 percent of PCs are related to genetics." was removed as the authors found it to be confusing for the readers.

2. (Line 109) as the aggressive or palliative care approach could be applied based on the "same": Based on the "stage"?

Re: Correct, change made and marked in red.

3. (Lines 209-211) PPAD (Porphyromonas Peptidyl Arginine Deaminase) 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]: Please make a brief explanation how PPAD affects P53 activity and causes K-ras mutation.

Re: Sentences were added please refer to lines 210-213.

"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 (GTP), can lead uncontrolled and inappropriate cell proliferation, thus increasing the risk of malignancy [52]."

4. (Lines 261-262) Furthermore, bile acids can modulate the composition of the microbiome and facilitate bacterial translocation into tissues,: According to the cited reference, I assume that loss of bile acid facilitate bacterial transocation.

Re: Yes, that is correct.

5. (lines 316-318) In a mice model, a "special group" represented the mice with a defective Toll-like receptor (TLR) signaling pathway, demonstrating no response to oxaliplatin treatment.: What is a "special group"? And, please cite a reference.

Re: Thank you for this observation.

The sentence was meant to say "In a mice model, a group with a defective Toll-like

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receptor (TLR) signaling pathway, demonstrated no response to oxaliplatin treatment [92]. "Lines 318-319. And the reference was added.

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Reviewer's code: 04091933

SPECIFIC COMMENTS TO AUTHORS

The topic of the manuscript is generally relevant and concerns the role of the gut microbiome in pancreatic cancer (PC).

Re: Thank you very much for recognizing the relevance of the topic and the hard work put together by the authors.

The manuscript as a whole is well written, but a number of important points need to be clarified.

Re: Thanks again for this observation.

1. The mechanisms by which the microbiota modulates carcinogenesis in PAC, such as the role of natural killers, are poorly understood (Yu Q et al, 2022). It is desirable to show how the fecal microbiota may influence the course and survival/outcomes in PC.

Re: The authors agree with this observation, the works by Riquelme et al. and Yu q et al., were added with relevant information.

"As evidence by the work of Riquelme et al [a,b], 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 [a,b]. 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 [a,b]."

"Natural killer (NK) cells are a group of cells that play an important role by mediating

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tumor initiation and progression. NK cells are often found in the circulation, preventing tumor cells from metastasizing [c,d]. When a patient is NK cells depleted, tumor escape and growth may ensue [c]. 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 [c]".

2. The possible role of fungi (mycobiota) (there is only one reference) and the virome (no references) in the pathogenesis of PC has not been disclosed.

Re: More references were added for fungi and virome.

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 (MBL), which binds to glycans of the fungal wall may lead to activation of the complement cascade and oncogenic progression [e].

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 (HBX), thus leading to oncogenesis [f].

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 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 [o].

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3. It is required to significantly supplement the information on the involvement of bacterial metabolites (SCFA, including butyrate, tryptophan metabolites, etc.) in PC oncogenesis and in response to treatment.

Re: Thank you for the observation, changes were made as outlined below.

Short-chain fatty acids (SCFA) which are metabolites from the gut microbiota and cathelicidin-related antimicrobial peptides (CRAMP) secreted by normal pancreatic β-cells protect against tissue inflammation and control pancreatic bacterial overgrowth [g,h]. 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 [i]. 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 [i]. Another SCFA from the GI microbiota, acetate, induces insulin secretion via the microbiome–brain β-cell axis controlling pancreatic bacterial overgrowth [j,k]. Tryptophan metabolism can serve as an immunomodulatory factor by overexpression of Indoleamine2,3-dioxygenase1 (IDO1) 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 (AhR), 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 [l,m,n].

4. The claim that Fusobacteria is associated with a reduced risk of pancreatic adenocarcinoma may be misleading to the reader. It is required to add the specific Leptotrichia genus associated with risk reduction, as other genera and species (eg

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Fusobacterium nucleatum) may conversely be associated with increased risk.

Re: Thank you very much for this keen observation. This was clarified in the amnuscript.

5. Not enough references 2022 (only 6) and 2023 (none).

Good observation to improve the overall quality of the manuscript. We added 7 more citations from 2023 and 3 more citations from 2022, bringing the 2022/2023 citations to 16. Thus, we are confident that we have enough up to date references.

6. The lack of illustrative material in the review is depressing. It is advisable to add a table and/or figure on the topic of the manuscript, for example, mechanisms of microbiota involvement or microbiota changes associated with PC).

Re: Another great point to improve the quality of the paper. We added two tables that can be found in the revised version.

7. Many taxa have outdated names (for example, Proteobacteria, Firmicutes, Fusobacteria, Bacteroides vulgatus, Bacteroides dorei, Lactobacillus casei, etc) We strongly recommend using a modern taxonomic classification (primarily for recently reclassified phyla and taxa). Old and incorrect names should be corrected to valid ones (eg Bacillota instead of Firmicutes, Fusobacteriota instead of Fusobacteria, Pseudomonadota instead of Proteobacteria). Please see: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijsem.0.005056. Please use italics for taxa and correct spelling errors in taxa and abbreviations (for example, Helicobacter Pylori, Staph. A, Porphyromonas Gingivalis, etc). Please also correct other grammatical errors/typos, for example, replace pancreatic CA with pancreatic cancer or PC, etc. After a major revision, the manuscript may be

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recommended for publication.

Re: Thanks again, we italicized all the taxa, and the suggested changes have been made. All changes are marked in red.

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