



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 75137

Title: Tumor Microenvironment in Pancreatic Ductal Adenocarcinoma: Implications in Immunotherapy

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05123031

Position: Editorial Board

Academic degree: Doctor, MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2022-01-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-16 23:33

Reviewer performed review: 2022-01-28 01:34

Review time: 11 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Manuscript Number: 75137 Title: Tumor Microenvironment in Pancreatic Ductal Adenocarcinoma: Implications in Immunotherapy Pancreatic ductal adenocarcinoma (PDAC) occurs in the exocrine compartment of the pancreas and accounts for approximately 90% of pancreatic malignancies, making it the most common pancreatic tumor. Due to lack of early diagnosis and limited response to treatment, PDAC remains a highly aggressive and lethal malignancy, the fourth leading cause of cancer-related death worldwide. The difficulty in treating pancreatic cancer is at the cellular and genetic levels. Mutations in pancreatic tumors can lead to genetic instability, tumor growth and resistance to therapy. In addition to typical molecular markers, including oncogenic KRAS mutations and inactivation of the tumor suppressor genes CDKN2A/P16, TP53, and SMAD4, PDACs frequently contain mutations involved in multiple cellular signaling pathways. Molecular heterogeneity may account for its resistance to chemotherapy. In addition, pancreatic cancer stem cells account for approximately 1% of all pancreatic cancer cells, have the ability to self-renew, and exhibit chemoresistance. Immunotherapy has emerged as one of the most promising treatment options for advanced solid tumors, including lung, kidney, bladder, liver, and colorectal cancers. Unfortunately, PDAC is significantly resistant to immunotherapy, and so far, most phase I/II clinical trials of PDAC have failed to demonstrate the ideal clinical efficacy of immunotherapy. Notably, microsatellite instability (MSI), one of the predictive biomarkers for immune checkpoint blockade therapy, was detected in only a very small number of PDAC patients (less than 1%). On the other hand, emerging evidence suggests that the tumor microenvironment (TME) in PDAC is a key component



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Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

of immunotherapy resistance. Despite advances in translational research, PDAC remains a highly lethal malignancy. Recent breakthroughs in immunotherapy have revolutionized cancer treatment and show great potential to transform the treatment of PDAC in the future. However, PDAC is less effective for various immunotherapies than other types of cancer. TME is considered a fundamental barrier to treatment resistance. To overcome this resistance, further research into innovative therapeutic strategies is required. This review provides a reference for immunotherapy in the treatment of pancreatic ductal adenocarcinoma. It has guiding significance to clinical work. Overall, I think this is a worthy review that has important implications. The manuscript can be accepted and published in World Journal of Gastroenterology.



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Peer-review model: Single blind

Reviewer's code: 05260764

Position: Peer Reviewer

Academic degree: Doctor, MD

Professional title: Surgeon

Reviewer's Country/Territory: Denmark

Author's Country/Territory: United States

Manuscript submission date: 2022-01-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-29 15:19

Reviewer performed review: 2022-02-01 21:12

Review time: 3 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This is a very good idea for a review article, since both tumor microenvironment in PDAC and immunotherapy are on the uprise as potential target and treatment options, and it is clear, that the authors have put a great deal of effort into writing this article. However, there are some fundamental flaws with this manuscript. T - The language is inconsistent regarding frases, abbreviations and uses "everyday language" too much. - The description of the different studies which the authors bases most of their review on, is messy, inconsistent and very hard to conclude anything from. - The composition of the manuscript could be made more streamlined - both for the readers but also for the general purpose of the article. Instead of explaining every type of pre-clinical and clinical studies regarding every type of target, therapy and vaccine, consider to compress it a little and focus on the overall picture for each of the subsections in the article. That would make the article much more useful as a an overview of the knowledge regarding PDAC, TME and immunotherapy for clinicians. Therefore, with some revisions, this could be a well written article of great interest to most who deals with not only PDAC patients, but cancer patients in general.



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Peer-review model: Single blind

Reviewer's code: 03261315

Position: Editorial Board

Academic degree: FACE, PhD

Professional title: Academic Research, Chief Doctor, Doctor, Postdoc, Professor, Senior Researcher

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2022-01-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-29 09:17

Reviewer performed review: 2022-02-07 10:20

Review time: 9 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The paper is well structured and easy to follow. The methodology of the paper is not described. In my opinion the paper is too long for a minireview and is more suitable for World Journal of Gastrointest Oncology. The legend for figure 1 is missing. There are some typing errors.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer’s code: 05260764

Position: Peer Reviewer

Academic degree: Doctor, MD

Professional title: Surgeon

Reviewer’s Country/Territory: Denmark

Author’s Country/Territory: United States

Manuscript submission date: 2022-01-16

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2022-04-29 06:25

Reviewer performed review: 2022-04-29 11:40

Review time: 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have done a great job revising this manuscript, especially regarding language and formate of the paper. It is now easy to read, relevant and can be used as a tool for clinicians every to get a better understanding and knowledge about the role of immunotherapy and TME in PDAC.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Professional title: Academic Research, Chief Doctor, Doctor, Postdoc, Professor, Senior Researcher

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2022-01-16

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2022-05-01 14:36

Reviewer performed review: 2022-05-02 11:16

Review time: 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

I re-reviewed the paper. It was difficult to compare the first version with new version . The modified phrases were not highlighted. However, it seems that the authors did not made any modifications in order to shorten the paper and compress it and focus on overall picture.