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https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Jundishapur Journal of Microbiology
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Published in: Jundishapur Journal of Microbiology: 13(9); e101137

Peer Review Report for "Adhesin HpaA of *Helicobacter pylori* Promoted Migration of AGS Cells via IL-21 Secretion From HpaA-induced CD4^{+}T Cells"

Author(s): Xianru Xia, Ying Hua, Pei Hu, Jie Li, Guolin Hu, Xiaolei Tang

Review Timeline:

Submit Date: 18 Mar 2020
Revised Date: 12 Oct 2020
Accepted Date: 1 Nov 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

26 May 2020

Dear AE,

The present study suggested that adhesin HpaA from H. pylori during infections plays a significant role in the process of gastric carcinoma cell metastasis. Although the topic is of interest to the Jundishapur Journal of Microbiology, the manuscript and study have some flaws. However, the bacterial isolation process is not clear, and details are missing, and it seems the identification of H. pylori isolates was subjective. The authors should provide more primary data. The other major flaw is in English Language and formatting errors throughout the manuscript.

1. Provide a structured abstract with the following headings: Background, Methods, Results, and Conclusions.
2. Mention the inclusion and exclusion criteria by details (in the material and methods).
3. In the “Patients’ Specimens” section, please add the number of samples in each group.
4. The number of total samples collected by authors is missing.
5. Some sections are need reference such as “CD4+T-cell immunopurification and purification of recombinant HapA fusion protein, while no reference has been mentioned.
6. Start the discussion by presenting your main findings.

7. No limitations of the study are indicated. Please add “limitation and suggestions at the end of the paper.
Thanks.

Farhad Safarpoor Dehkordi: Reviewer | **Revision (0)** 3 Jun 2020

Dear AE,
Well, this is an original research work about the Adhesin HpaA of Helicobacter pylori promoted migration of AGS cells via IL-21 secretion of HpaA-induced CD4+T cells. The basic title and information are so interesting. Authors declared that higher levels of IL-21, MMP-2, and MMP-9 in patients’ biopsies with H. pylori infection than post-eradicating. The level of IL-21 from CD4+ T cells and cultural supernatant increased with the recombinant HpaA treatment, and then the AGS cells expressed a high level of MMP-2, MMP-9, and metastasis by co-cultured with aforesaid CD4+ T cells. Our previously reported aptamers HA6, specific binding, and blocking HpaA, and anti-IL-21 mcAb remarkably reduced the AGS cell migration via reduced the level of IL-21 directly or indirectly. Our research suggested that adhesin HpaA plays a significant role in the process of gastric carcinoma cell metastasis through IL-21 from HpaA-induced T cells and aptamers may be a potential therapeutic agent for H. pylori treatment.
However, this is an interesting work, but authors should address the following comments before its full acceptance.
1- Some parts of the text are full of grammatical and typographical mistakes. Please use from a native English speaker person who is an expert in microbiology to revise your text.
2- The authors said: The samples were categorized into two groups, the H. pylori-positive group, and the corresponding H. pylori-radication group…. How did you determine the H. pylori-positive group?
3- The authors said: None of the H. pylori-positive patients had undergone treatment of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or proton pump inhibitors… What about other choices of treatment of Helicobacter pylori infections?
4- Please add more details about Quadruple therapy.
5- Authors used from H. pylori-specific ureC PCR for the identification of H. pylori strains. However, some novel works revealed that some of the pathogenic strains of this bacterium didn’t have urease activity. Thus, authors may fail to detect all of the H. pylori strains.
6- How did the authors prepare microaerophilic conditions?
7- How the H. pylori was collected at the logarithmic phase?
8- How the quality and quantity of RNA were measured?
9- How the purity of extracted cDNA was measured?
10- Please add more details for the primers in Table 1.
11- Please add the positive and negative controls in the PCR reactions.
Thanks.

Farhad Safarpoor Dehkordi: Associate Editor | **Revision (0)** 3 Jun 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) 4 Jun 2020

Dear Author,

Thank you for submitting your manuscript to JJM. I have completed the review of your manuscript and a summary is appended below (Pleases find attached files). The reviewers recommend the reconsideration of your paper following major revision. I invite you to resubmit your manuscript after addressing all reviewer comments. Please answer point by point to reviewer's comments on a separate sheet under WORD format and write your modifications in the revised version (WORD format) in colored or highlighted letters. Your answers to reviewers' queries are not only for the Editorial Board but for the readers and should be included, when appropriate, in the manuscript for improvement and a better understanding.

When resubmitting your manuscript, please carefully consider all issues mentioned in the reviewers' comments, outline every change made a point by point, and provide suitable rebuttals for any comments not addressed. In addition, JJM INSTRUCTION attached to the mail, Pleases find it.

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Thanks.

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Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear editor,
Thanks for yournice comments on our article. According to your suggestions, we have supplemented table 2 and corrected article structure, especially the references, in our previous draft. Based on your comments, we have made extensive revisions to our previous draft. The table 1 and table 2 were presented in resubmission manuscript. Meanwhile the EIC file in Chinese was uploaded by separate file.
Appreciate your time and will await for your response.

Best regards,
Tang xiaolei

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision (1)** 31 Aug 2020

Dear Authors,
Please answer point by point to the reviewer's comments on a separate sheet under WORD format and write your modifications in the revised version (WORD format) in colored or highlighted letters.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear editor,

Because my false operation on author's panel, I am very sorry for belated revision status. Thanks for your and the other two reviewers' nice comments on our article. According to your suggestions, we have supplemented several data here and corrected several mistakes in our previous draft. Based on your comments, we also attached a point-by-point letter to you and the other two reviewers. We have made extensive revisions to our previous draft. The detailed point-by-point responses are listed below. The table 1 was presented in resubmission manuscript.

Appreciate your time and will await for your response.

Best regards,

Corresponding Author:Tang xiaolei

Reviewer 1:

The present study suggested that adhesin HpaA from H. pylori during infections plays a significant role in the process of gastric carcinoma cell metastasis. Although the topic is of interest for Jundishapur Journal of Microbiology, the manuscript and study have some flaws. However, the bacterial isolation process is not clear, and details are missing, and it seems the identification of H. pylori isolates was subjective. The authors should provide more primary data. The other major flaw is in English Language and formatting errors throughout the manuscript.

1. Provide structured abstract with following headings: Background, Methods, Results, and Conclusions.

Thanks for your guidance. We have modified the structure of this paper according to four headings.

2. Mention the inclusion and exclusion criteria by details (in the material and methods).

The inclusion criteria was added on 18th line of 5th page in this paper. The gastric mucosa was main research object, so the results of rapid urease test was main basis of inclusion and exclusion.

3. In the "Patients' Specimens" section, please added the number of samples in each group.

The number of samples was added on 2nd line of 6th page in this paper. Of course, more than 112 pieces specimens were gained from study, because the two or more pieces were taken out for diagnosis. But in our study, two pieces of gastric mucosa from 56 donors were selected and researched from each patient, before and after treatment.

4. The number of total samples collected by authors is missing.

Thanks for your advice. The presentation in previous article was not very clear, but it had been corrected. The number of samples was added on 2nd line of 6th page in this paper. Of course, more than 112 pieces specimens were gained from study, because the two or more pieces were taken out for diagnosis. But in our study, two pieces of gastric mucosa were selected and researched from each patient, before and after treatment.

5. Some sections are need reference such as "CD4+T-cell immunopurification and purification of recombinant HapA fusion protein, while no reference has been mentioned.

Thanks for your comments. The two references were added on the 10th line of 7th page

and the 3rd line of 7th page in this paper. The two references were labelled as (17) and (18) with yellow shade.

6. Start the discussion by presenting your main findings.

Thanks for your advice. We had modified the presentation structure of discussion and the our main findings were in begin of our discussion.

7. No limitations of the study are indicated. Please add “limitation and suggestion in the end of paper.

Thanks for your guidance very much. That is what I've been thinking about when I do research. So I added my idea, from the 3rd line of 16th page and the 12th line of 16th page, about the flaw and uncovered field in this research. We only represented a phenomenon trough a line, from adhesin HpaA to IL-21 and from IL-21 to AGS cells migration.

Reviewer 2:

Journal: Jundishapur Journal of Microbiology

Type: Research Article

Manuscript Full Title: Adhesin HpaA of Helicobacter pylori promoted migration of AGS cells via IL-21 secretion of HpaA-induced CD4+T cells

Manuscript number: 100348

Well, this is an original research work about the Adhesin HpaA of Helicobacter pylori promoted migration of AGS cells via IL-21 secretion of HpaA-induced CD4+T cells. The basic title and information are so interesting. Authors declared that higher levels of IL-21, MMP-2, and MMP-9 in patients’ biopsies with H. pylori infection than post-eradicating. The level of IL-21 from CD4+ T cells and cultural supernatant increased with the recombinant HpaA treatment, and then the AGS cells expressed a high level of MMP-2, MMP-9, and metastasis by co-cultured with aforesaid CD4+ T cells. Our previously reported aptamers HA6, specific binding, and blocking HpaA, and anti-IL-21 mcAb remarkably reduced the AGS cells migration via reduced the level of IL-21 directly or indirectly. Our research suggested that adhesin HpaA plays a significant role in the process of gastric carcinoma cell metastasis through IL-21 from HpaA-induced T cells and aptamers may be a potential therapeutic agent for H. pylori treatment.

However, this is an interesting work, but authors should address the following comments before its full acceptance.

1- Some parts of the text are full of grammatical and typographical mistakes. Please use from a native English speaker person who is an expert in microbiology to revise your text.

Thanks for your advice. The presentation in previous article was not very clear, but it had been corrected. Please check it and will you be kind enough to prune.

2- The authors said: The samples were categorized into two groups, the H. pylori-positive group and the corresponding H. pylori-radication group…. How did you determine the H. pylori-positive group?

The infection status was analyzed using the rapid urease test, 14C Urea breath tests and *H. pylori*-specific ureC PCR. If any two or more items were positive, the result was determined H. pylori-positive.

3- The authors said: None of the H. pylori-positive patients had undergone treatment of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or proton pump inhibitors… What about other choices of treatment of Helicobacter pylori infections?

None of the H. pylori-positive patients had undergone treatment of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or proton pump inhibitor at least one month prior testing. Of course, that was what we agreed with them in advance.

4- Please add more details about Quadruple therapy.

Quadruple therapy, treat helicobacter pylori infection in China, involves a proton pump inhibitor, such as Omeprazole or Pantoprazole, or Lansoprazole or Rapeazole,

combined with two antibiotics, such as Clamycin, Amoxicillin, Metronidazole and Levofloxacin, plus a Bismuth agent, such as colloid Bismuth. In this way, the H.pylori can be removed in about 14 days for the majority of patients with H.pylori infection.

5- Authors used from H. pylori-specific ureC PCR for the identification of H. pylori strains. However, some novel works revealed that some of the pathogenic strains of this bacterium didn't have urease activity. Thus, authors may fail to detect all of the H. pylori strains.

The infection status was analyzed using the rapid urease test, pathological staining, 14C Urea breath tests and *H. pylori*-specific ureC PCR. The two or more positive terms of above four methods of every donors was confirmed *H. pylori* infection.

6- How did authors prepare microaerophilic conditions?

The microaerobic tank and gas bags, purchased from *Mitsubishi corporation* of Japan, were combined to form the microaerobic environment.

7- How the H. pylori was collected at the logarithmic phase?

The 10^8cfu *H. pylori* was loaded and cultured in 50 mL fluid nutrient medium (no containing sheep blood) in stable microaerobic environment and the OD_{600nm} of bacteria solution turbidity was detected continuously. When the OD_{600nm} reached to 0.6 approximately, this status was taken for logarithmic phase according to growth curve, our drawn curve previously.

8- How the quality and quantity of RNA were measured?

The all gastric mucosa specimen were preserved in a preservation solution, containing RNA protection ingredient, purchased from ThermoFisher (RNA laterTM). Total RNA was extracted using total RNA extraction kit (Cat#:1218325, ThermoFisher). The the quality and quantity of extracted total RNA were measured using the commercial kits (Cat#:Q33221, for quality detection and Cat#:Q33223, for quantity detection , ThermoFisher) and nucleic acid quantifier (Qubit Flex fluorimeter , ThermoFisher).

9- How the purity of extracted cDNA was measured?

The purity of extracted cDNA was measured by commercial kit and ssDNA quantifier (QuantiFluor® ssDNA system, Promega).

10- Please add more details for the primers in Table 1.

The annealing temperature of primers and amplification length of products were added in Table 1.

11- Please add the positive and negative controls in the PCR reactions.

In this study, the no template of PCR system was used as negative controls and positive template of four indicators come from our previous research. The above description was used to control experiment quality, avoiding false negatives and false positives.

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Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (2) 1 Nov 2020

Dear Authors
According to the associated editor report, your manuscript is accepted for publishing in JJM and send to the publisher for the next process.
Note:
Please add ORCID number into you and your collages account, then automatically appear in your published papers in JJM both in HTML and pdf.
Thanks.