



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47301

Title: Multiplex gene expression profile in inflamed mucosa of surgical patients with Crohn’s disease ileal localization

Reviewer’s code: 03254999

Reviewer’s country: United States

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-22 13:32

Reviewer performed review: 2019-04-22 20:05

Review time: 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input checked="" type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The article language needs some polishing, especially the grammar. This is an interesting topic but perhaps too much at the basic science level for this journal. I think this would be potentially a good article for another journal.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47301

Title: Multiplex gene expression profile in inflamed mucosa of surgical patients with Crohn's disease ileal localization

Reviewer's code: 00503587

Reviewer's country: New Zealand

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-23 01:43

Reviewer performed review: 2019-04-28 00:32

Review time: 4 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
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		<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This MS focuses on the expression of key genes in patients with CD who had undergone a resectional surgery

SPECIFIC COMMENTS

1. The term "surgical patients" in the title would be better replaced.

Following the revisors' suggestion, we erased the term "surgical" in the title



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2. The methods section of the ABSTRACT and the main METHODS section of the MS both contain patient numbers and details that are results - these should be moved accordingly.

The abstract also includes unexplained abbreviations

As suggested, we deleted patients number in the method section of the abstract and moved them to the result section (line 119). About methods in the main section, we reported the number of the patients only as usually the methods section is also called patients and methods: however, if you think it is not the appropriate section to introduce the patients we are ready to modify it, as well as the data and details you believe should be considered as results (please specify them, thanks). We explained the abbreviations used in the text: Light microscopy (LM) and Transmission Electron Microscop (TEM) (line 115)

3. The conclusion of the ABSTRACT is very awkward and unclear - this should be revised and rewritten We thank the reviewer for the suggestion, we reframed the abstract conclusion (from line 127 to line 130)

4. The patterns of disease location mentioned in the INTRO are reasonable and appropriate. Age-related differences are relevant as are genetic differences (and related ethnic differences).

We agree with the reviewer

5. This study relates just to the setting of ileal disease location. It transpires however, that some patients did not have active (inflamed) ileal disease when resected, and so these samples were used to compare to inflamed areas. It was not clear why a patient would've had a resection of non-inflamed ileal tissue? Also, the authors argue that the ileal location is a master controller of responses there and more distally - this argument would've been much stronger to defend if the current work had included additional aspects such as colonic tissue responses.

The patients operated for ileal Crohn's disease underwent bowel resection removing the diseased intestinal tract along with a short segment (of about 5 cm) both upstream and downstream of the lesions. The last samples were considered as the non-inflamed sample and were used for



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comparison with those taken from the diseased section. To make clear the method that we have adopted, we have replaced the sentence on page 9, line 181 with the following:

“The surgical specimen was opened longitudinally. Tissue samples were taken both from the tract affected by Crohn's disease and from the apparently healthy and disease-free margins”

We included additional aspects such as colonic tissue responses. We believe these changes, associated to a complete English revision of the text, allow to understand in a clearer way that the study was conducted on the same 14 patients affected by CD terminal ileitis and from their surgical specimen we obtained and analysed both ileal diseased (one) and ileal healthy (another one) samples. The healthy sample was usually obtained from the surgical resection margin. About colonic controls, as yet explained above, we compared the results obtained in this 14 ileal CD patients, with the results obtained in 14 patients affected by colonic CD previously studied with the same technique (manuscript cited in the reference section at number 10).

6. the METHODS section mentions control subjects in passing but does not mention the methods of recruitment of these patients

As suggested by the reviewer, we specify the methods of recruitment from line 167 to 168

7. In terms of reporting the NOD2/CARD 15 genetic data do the authors mean that only 4 of the 12 patients had one polymorphism? A lower rate than expected. The use of the 1/3 in this section is confusing

As suggested by the reviewer, from line 302 to 304 we modified the text in order to avoid the confusion

8. It was not clear what the morphological analyses added to the study, as this did not focus on specific gene outputs or other direct connections to the genetic analyses?

We think that the microscopic anatomy analysis aims to provide some details that illustrate phenotypic features. Although these morphological traits are not directly related to specific gene outputs, they illustrate the tissue responses to key gene deregulation (from line 399 to line 404)



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9. Does tonaca propria mean lamina propria?

Yes, the two words are synonyms, if the reviewer prefers “lamina propria”, we have already replaced it in the text. (Actually, *tonaca (tunica) propria* is an old fashion *nomen anatomicum*: it is been replaced by lamina propria.)

10. The title for table 1 should be:patients with ileal CD...

Thank you for the suggestion, we corrected the title of Table 1

11. K+ and prK+ are not explained in Table 1

We erased the two abbreviation, as we think they are not relevant for the Table 1 .

12. The title for Table 2 could be improved

We improved the title, as suggested

13. There are a number of English language errors (grammar, word use, word structure)

We corrected grammar, word use and word structure

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47301

Title: Multiplex gene expression profile in inflamed mucosa of surgical patients with Crohn’s disease ileal localization

Reviewer’s code: 03478442

Reviewer’s country: Greece

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-22 09:45

Reviewer performed review: 2019-04-30 08:50

Review time: 7 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting original article, investigating certain genes expression in ileal CD with the help of an innovative approach. Despite the small number of patients and minor grammatical errors, this is a well-prepared manuscript adding valuable information on our understanding of the complex pathogenetic mechanisms of IBD.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47301

Title: Multiplex gene expression profile in inflamed mucosa of surgical patients with Crohn's disease ileal localization

Reviewer's code: 02978709

Reviewer's country: Denmark

Science editor: Ruo-Yu Ma

Reviewer accepted review: 2019-04-28 02:03

Reviewer performed review: 2019-05-05 08:48

Review time: 7 Days and 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
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			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The article provides an analysis of mRNA levels for selected genes for identification of colonic and/or ileal Crohn's disease. The idea is good. The sample is very small therefore the study must be regarded as a pilot study. This must be stated in the title.

Thank you for the suggestion, we added "pilot study" in the title



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Some major changes are needed:

Abstract: The conclusion cannot start with “thus remaining..etc”. Indicate in a short sentence what was the conclusion of the study.

As suggested by the reviewer, we erased “thus remaining.etc” in line 95

Introduction: The readers of this journal are aware of IBD therefore no need to state this. I suggest to delete the first sentence in the introduction “inflammatory bowel disease includes two major....pathogenesis of the disease”.

We thank the reviewer for the appropriate suggestion, we erased the first sentence (from line 116 to 118)

Paragraph 2: what do you mean by ileal inflammation are not superimposable? Please reformulate the sentence.

As suggested, we reformulate the sentence: “In addition, the immunological pathways involved in colonic inflammation are different from those involved in ileal inflammation” (from line 135 to line 137)

Paragraph 4 “In this study, we developed...etc” this belongs to the method and not introduction.

We thank the reviewer for the suggestion, we erased the sentences belonging to method and not introduction (from line 148 to line 149)

Method: Some language and typos minor changes are needed. Please, read it through again with a help of a native speaker.

We corrected the language errors

Results: Discussion: First paragraph “CD issuch dysregulation” belongs to the introduction if it is necessary. I think it is a repetition that can be deleted. The authors need to discuss their results in the light of existing literature.

We erased the sentence “CD issuch dysregulation”, as suggested by the reviewer (From line 419 to line 428)



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The phrase “did not reach statistical significance” must be avoided see please Altman et al recommendations.

We erased the phrase “did not reach statistical significance” as suggested by the reviewer (line 378-line 379)

There is a need for a paragraph on study limitations and perspectives.

As suggested by the reviewer, we wrote a paragraph on study limitations (from line 382- to line 391): “Our study presents main limitations related to the low number of subjects investigated which may have influenced the statistical power of the study. To confirm these results, studies with a larger number of patients are needed. In addition, gene expression was evaluated only with Multiplex Gene Assay. This method directly quantifies the mRNA amounts without need of reverse transcription and gives a detailed picture of the inflammation process for each patient but it should be validated by comparisons with additional techniques to evaluate gene expression”.

We also added the research perspective paragraph (line 416-428)

Conclusion 26 lines of words! Conclusion must be a short statement (2-3 lines only) of what the authors found in their study. There is so much repetition to what the authors already mentioned in the introduction.

As suggested, we shortened the conclusion by leaving the most relevant sentences (from line 417- to line 438)

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