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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47633

Title: Helicobacter pylori and cytokine gene variants as predictors of premalignant gastric lesions

Reviewer's code: 00717554

Reviewer's country: Netherlands

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-03 17:37

Reviewer performed review: 2019-04-03 17:55

Review time: 1 Hour

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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced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

SPECIFIC COMMENTS TO AUTHORS

I would like to mention the following comments: 1- The first sentences of abstract (fifth) and introduction (third) are confusing, although one is death and one is diagnosed. 2- Epidemiology: incidence and mortality rates are missing. 3- It might be better to

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explain the different parts of text to at least 3 parts. 4- Table 1: Statistical methods or models? It is just methods and the name of tests. Good Luck

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47633

Title: Helicobacter pylori and cytokine gene variants as predictors of premalignant gastric lesions

Reviewer's code: 00058340

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-04 06:59

Reviewer performed review: 2019-04-08 00:13

Review time: 3 Days and 17 Hours

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

SPECIFIC COMMENTS TO AUTHORS

The authors reviewed the role of cytokines and their gene variants in regard to non-self-limiting H. pylori gastritis and its evolution to gastric atrophy and intestinal metaplasia; the literature now includes various and non-conclusive results on this topic.

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While the influence of the majority of cytokine single nucleotide polymorphisms has been investigated for gastric cancer it was not examined for preneoplastic gastric lesions. Amongst the investigated gene variants only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were identified as predictors for premalignant gastric lesions risk. Comments. `1. The review is good and comprehensive but in order to provide a more in depth insight and a full picture the authors should add important information as follow: a) Gastric intestinal metaplasia (IM) and gastric cancer are associated with Helicobacter pylori, but the bacterium often is undetectable in these lesions. However, H. pylori and its genes were detected inside metaplastic, dysplastic, and neoplastic epithelial cells, and cagA and babA2 expression was colocalized. The preneoplastic "acidic" MUC2 mucin was detected only in the presence of H. pylori, and MUC2 expression was higher in patients with IM, dysplasia, and cancer. These findings are compatible with the hypothesis that all stages of gastric carcinogenesis are fostered by persistent intracellular expression of H. pylori virulence genes, especially cagA inside MUC2-producing precancerous gastric cells and pleomorphic cancer cells. Semino-Mora C, et al. Intracellular and interstitial expression of Helicobacter pylori virulence genes in gastric precancerous intestinal metaplasia and adenocarcinoma. J Infect Dis. 2003 Apr 15;187(8):1165-77. PMID: 12695995 b) Important studies, e.g. one cited below demonstrated that chronic infection of C57BL/6 mice with Helicobacter, a known carcinogen, induces repopulation of the stomach with BMDCs. Subsequently, these cells progress through metaplasia and dysplasia to intraepithelial cancer. These findings suggest that epithelial cancers can originate from marrow-derived sources and thus have broad implications for the multistep model of cancer progression. Several cytokines are critical for recruitment of bone marrow-derived progenitor cells. Houghton et al. Gastric cancer originating from bone marrow-derived cells. Science. 2004 Nov 26;306(5701):1568-71. c)

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accumulating evidence indicates that stem cells are the major cellular origin of most cancers, including gastric cancer. Hayakawa Y et al. The Origins of Gastric Cancer From Gastric Stem Cells: Lessons From Mouse Models. Cell Mol Gastroenterol Hepatol. 2017 May; 3(3): 331–338. PMID: 28462375 The authors reviewed the role of cytokines and their gene variants in regard to non-self-limiting H. pylori gastritis and its evolution to gastric atrophy and intestinal metaplasia; the literature now includes various and non-conclusive results on this topic. While the influence of the majority of cytokine single nucleotide polymorphisms has been investigated for gastric cancer it was not examined for preneoplastic gastric lesions. Amongst the investigated gene variants only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were identified as predictors for premalignant gastric lesions risk. Comments. `1. The review is good and comprehensive but in order to provide a more in depth insight and a full picture the authors should add important information as follow: a) Gastric intestinal metaplasia (IM) and gastric cancer are associated with Helicobacter pylori, but the bacterium often is undetectable in these lesions. However, H. pylori and its genes were detected inside metaplastic, dysplastic, and neoplastic epithelial cells, and cagA and babA2 expression was colocalized. The preneoplastic "acidic" MUC2 mucin was detected only in the presence of H. pylori, and MUC2 expression was higher in patients with IM, dysplasia, and cancer. These findings are compatible with the hypothesis that all stages of gastric carcinogenesis are fostered by persistent intracellular expression of H. pylori virulence genes, especially cagA inside MUC2-producing precancerous gastric cells and pleomorphic cancer cells. Semino-Mora C, et al. Intracellular and interstitial expression of Helicobacter pylori virulence genes in gastric precancerous intestinal metaplasia and adenocarcinoma. J Infect Dis. 2003 Apr 15;187(8):1165-77. PMID: 12695995 b) Important studies, e.g. one cited below demonstrated that chronic infection of C57BL/6 mice with Helicobacter, a known

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carcinogen, induces repopulation of the stomach with BMDCs. Subsequently, these cells progress through metaplasia and dysplasia to intraepithelial cancer. These findings suggest that epithelial cancers can originate from marrow-derived sources and thus have broad implications for the multistep model of cancer progression. Several cytokines are critical for recruitment of bone marrow-derived progenitor cells. Houghton et al. Gastric cancer originating from bone marrow-derived cells. Science. 2004 Nov 26;306(5701):1568-71. b) accumulating evidence indicates that stem cells are the major cellular origin of most cancers, including gastric cancer. Hayakawa Y et al. The Origins of Gastric Cancer From Gastric Stem Cells: Lessons From Mouse Models. Cell Mol Gastroenterol Hepatol. 2017 May; 3(3): 331–338. PMID: 28462375

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47633

Title: Helicobacter pylori and cytokine gene variants as predictors of premalignant gastric lesions

Reviewer's code: 02954663

Reviewer's country: Hungary

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-02 04:22

Reviewer performed review: 2019-04-08 04:20

Review time: 5 Days and 23 Hours

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

SPECIFIC COMMENTS TO AUTHORS

The manuscript is a well-written narrative review on the role of cytokines - albeit a little bit exhaustive- and gastric premalignant conditions. The title and abstract are adequate, the keyword are well chosen and a main body of the manuscript is well systematized.

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However, the information is overwhelming and ther manuascript does not present the practical importance of cyítokine measurement. I strongly recommend to the authors to present and comment the following: a) is there any correelation between OLGA/OLGIM staging and level of any cytokine? b) is there anyí correelation between serologic bioosy (pepsinogen I/II nratio + H pylori + gastrin 127) and level of certain cytokines? c) what is the place of cytokine measurements - excepting research - in the routine diagnosis and management of precancerous conditoons;are these methods included in the most recent quidelines (ex. Nunes PP et al., Endoscopy, doi: 10.-1055/a-0859-1883)

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47633

Title: Helicobacter pylori and cytokine gene variants as predictors of premalignant gastric lesions

Reviewer's code: 02537773

Reviewer's country: Germany

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-14 10:53

Reviewer performed review: 2019-04-24 20:58

Review time: 10 Days and 10 Hours

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

SPECIFIC COMMENTS TO AUTHORS

The review deals with the topic of cytokine SNPs as predictors of premalignant gastric lesions. The topic may be of the interest to community focusing on this topic. Therefore, the idea to summarize the knowledge is important and timely. There are several

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issues that need to be addressed to make the data clear and at glance. 1) The current art of the tables demonstrates the data in reference-based way. This is misleading and not helpful to gain the overview (specifically table 2). 2) More detailed comparison between cohorts/patients/frequency for SNP by SNP approach is recommended. 3) The authors do not show the difference and similarities between the studies in SNP by SNP approach. 4) What is the impact of H. pylori (key impact factor) finally in SNPs? 5) Clear conclusions to the current knowledge and state of art is not provided. Minor comments: personally, I find the abbreviation of AG , CoAG and ChAG very confusing. Chronic gastritis is usually abbreviated by CG or NACG (non-atrophic chronic gastritis).

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