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8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30400
Title: Different phenotypes of monocytes in patients with new-onset mild acute pancreatitis
Reviewer's code: 03558529
Reviewer's country: United Kingdom
Science editor: Jing Yu
Date sent for review: 2016-10-08 18:40
Date reviewed: 2016-11-15 23:12

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a good study with detailed and well-performed phenotyping of monocyte populations which shows that changes to these populations can be detected early on in MAP pathogenesis, correlate well to clinical parameters (CRP) and may be a useful tool in diagnosis. The combination of markers used is unusual however the authors have found some interesting differences in monocyte subtypes which could have implications for MAP screening. Although monocytes and macrophages are already known to be important role in the pathophysiology of MAP, the use of new-onset patients in this study makes the findings particularly novel and significant. My concerns are listed below: My main concern is the confusion in the manuscript between monocytes and macrophages. The use of M1-macrophage and M2-macrophage to describe the cells analysed in this study is misleading and should be changed. The terms monocyte and macrophage are used interchangeably to describe the cells which is incorrect in this instance. The cells in this study (monocytes) are described as being M1-like or M2-like which is a property of macrophages, not monocytes. I presume this is why many of markers used for the study are actually typical for analysis of macrophages rather than monocytes.

In any case I think it would be more appropriate to refer to the cells in this study as pro-inflammatory and classical monocytes. Lines 115 to 117: 'Macrophages and monocytes are heterogeneous cell populations. Under an inflammatory condition, blood monocytes can maturate into macrophages, which are further activated.' It would be more accurate to state that monocytes are circulating blood cells which differentiate into macrophages when they enter the tissue. A lot of the introduction discusses M1 and M2 macrophages and their properties. However the present study investigates monocytes, not macrophages. Although monocytes can give rise to macrophages, they are not the same cell type, they have different cell markers and different activation states and properties. M1 and M2 polarization are properties of macrophages, not monocytes. It should be made clear in the text the difference between the two. For example line 143 'In this study, we characterized the numbers of different subsets of macrophages ' this is incorrect. Further discussion of monocyte subsets and markers should be given in the introduction, rather than macrophage subsets. I think that the use of M1 and M2 to describe the cells analysed in this study is misleading and should be minimized. A reasoning for the flow cytometry markers selected and gating strategy should be given. Monocytes are primarily distinguished by CD14 and CD16 as classical (CD14(++)CD16(-)), intermediate (CD14(++)CD16(+)) and nonclassical/pro-inflammatory (CD14(+)CD16(++)) monocytes. Why was CD16 omitted from this study? Why was CD163 used instead? It would be good to include the ratio between CD14+CD163- and CD14+CD163+ monocytes in Figure 1. The ratio between inflammatory vs non-inflammatory monocytes is as important as changes to overall number because they can balance each others actions. Figure 2. What is the percentage of CD14+CD163- cells which are positive for MAC387? Are there more CD14+CD163-MAC387+ cells in the MAP patients simply because there are more CD14+CD163- cells in the MAP patients? Or is a greater percentage of the CD14+CD163- expressing MAC387 in the MAP patients? Figure 4. I would like to see the mean fluorescence intensity of IL-10 and IL-12 in the various monocyte populations rather than the percentage positive. Here also the ratio between IL-10-positive and IL-12-positive would be informative. Figure 4. Were the monocytes expressing detectable levels of IL-10 or IL-12 in the absence of in vitro stimulation with LPS/PMA/ionomycin? This would be more relevant.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30400
Title: Different phenotypes of monocytes in patients with new-onset mild acute pancreatitis
Reviewer's code: 00069137
Reviewer's country: Mexico
Science editor: Jing Yu
Date sent for review: 2016-10-08 18:40
Date reviewed: 2016-11-17 19:28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[Y] No	

COMMENTS TO AUTHORS

The paper is interesting, well designed, and the idea behind the work is original. The paper is well written. I have some major comments and other minor comments 1. The authors mix terminology when discussing monocytes and macrophages. The cells studied appear to be monocytes. (PBMC) 2. The sample is quite small. While the matching seems adequate, the usual ratio of cases to controls is either 1:1 or ecen 1:2. 3. Were patients stratified according to pancreatitis etiology? would differences be expected from biliary, alcoholic, or triglyceride induced AP? 4. The discussion of interleukin levels as biomarkers seems out of context. The discussion of how IL levels could be related to monocyte subpopulations is interesting. However, there are other sources of IL-10 or IL-12 besides monocytes. 5. At what period in the evolution of pancreatitis were smaples drawn? 6. At times in the discussion results are repeated textually instead of discussed in relation to the relevant literature. 7. It would be interesting to study to what extent monocyte subpopulations change in relation to pancreatitis or inflammation in general. A group with inflammation from another source would be helpful. This would give a pathophysiologic link more plausability and specificity. 8. It

should be noted that a cause-effect association is difficult to establish. Are monocyte population changes a marker of inflammation (more likely)? or do they participate in pathogenesis (or repair??)?.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30400
Title: Different phenotypes of monocytes in patients with new-onset mild acute pancreatitis
Reviewer's code: 00456978
Reviewer's country: United Kingdom
Science editor: Jing Yu
Date sent for review: 2016-10-08 18:40
Date reviewed: 2016-12-09 06:19

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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COMMENTS TO AUTHORS

It reads as a fairly good manuscript and my comments are limited to some style, language and typos. page3 line75 - "were correlated": change to "correlated"; page5 line122-123 - "help to tissue repair, but promote tumor growth and metastasis": I guess it would be more correct to say "help immunoregulation and tissue repair but that may promote ...". Firstly, the phrase as it is creates an impression that all M2 macrophages are tumor-associated. Secondly, keeping in mind the "Colourwheel of the macrophage activation" (for example from http://www.macrophages.com/macrophage-review), it is important to mention the regulatory function of M2 macrophages; page 5 line 132 - "MAC387+ monocytes/macrophages are recently recruited into the tumor...": perhaps it is better to refer to those as "recently infiltrating monocytes/macrophages" (as in Ref13), since they may have other functions in addition to association with tumors; same for p.9 l.244; p.6 l.159 - "no a history" -> "no history"; p.8 l.230 - "in the patients" -> "in the MAP patients"; p.11 l.309 - "the numbers of of peripheral blood different subsets of macrophages" -> "the number of of different subsets of peripheral blood macrophages".

The study is generally well written, and in my opinion only few minor corrections need to be done.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 30400
Title: Different phenotypes of monocytes in patients with new-onset mild acute pancreatitis
Reviewer's code: 00947129
Reviewer's country: Hungary
Science editor: Jing Yu
Date sent for review: 2016-10-08 18:40
Date reviewed: 2016-12-09 23:30

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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Zhang et al. investigated the numbers of different subsets of monocytes and their associations with clinical markers of patients with mild acute pancreatitis (MAP). Overall, this is a nice stud; however, there are some points that need attention: 1. The terms monocytes and macrophages are used interchangeably. However, these cells are not the same. 2. The authors are investigating Map patients. Therefore, I do not quite understand one of their main conclusions: CD14+CD163+CD115+ macrophages (monocytes!) may be a biomarker for evaluating the severity of MAP. The severity of MAP by definition is mild. Even if a patient has higher CRP levels, the disease severity remains mild. The really interesting thing would be to include patients with moderate or severe disease. 3. The method of sampling needs to be described in more detail. How much blood was taken, in what type of tubes, from where? The time of sampling is also critical as MAP resolves quickly. 4. Also, more data is needed concerning MAP patient characteristics. What was the etiology, body mass index and length of hospital stay in these patients? 5. Figure legends are considered as stand-alone. The experimental protocol and abbreviations need to be defined here as well. I'm not an expert in flow

cytometry, so it was rather difficult for me to understand what the numbers mean in the SSC diagrams (e.g. 33.8 in top right panel of Fig. 1A). 6. Note you are measuring amylase and lipase "activities". 7. Superscripts and subscripts are missing in the manuscript (e.g. 106 cells in line #190, CO2 in line #193, in Table 1). 8. There are some sentences that need rephrasing (e.g. in line #308, activation degrees are associated the severity; in line 324, MAC387+ macrophages are recently recruited macrophages; in line 332, a positive feedback loop to strength pro-inflammatory responses). 9. Abbreviations should be defined at first use (e.g. CBA). Lipase is abbreviated as LPS in Table 1, but LPS is also defined as lipopolysaccharide on page 7. This is a bit confusing.