ANSWERING REVIEWERS

May 04, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10154-review.doc).

Title: IMMUNE-MODULATING THERAPY IN ACUTE PANCREATITIS: FACT OR FICTION

Author: Karolina Akinosoglou and Charalambos Gogos

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10154

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

(1) Reviewer 1 : Acute Pancreatitis is characterized by an acute, localized inflammatory response in the pancreas. This localized inflammatory response can become systemic and result in serious complications. Currently there is no therapeutic treatment for acute pancreatitis. This review summarizes studies that as a means of treating acute pancreatitis have attempted to reduce pancreatic inflammation. Numerous studies have been preformed both in preclinical animal models and clinical trials designed to decrease the inflammatory response associated with pancreatitis. Although much of it is dated, he authors do a good job in reviewing the literature. None of these studies has lead to the development of specific therapeutic interventions. The authors do an excellent job of reviewing the older literature. The weakness of this a review is not in reviewing in what has been done in the past, but what are the current areas being pursued. For example, there is very little information regarding Nf-κB. Numerous studies in the last 3-4 years have been preformed investigating the potential inhibition of the Nf-κB signaling during pancreatitis. These studies have employed both transgenic animals and development and testing of inhibitors of this pathway. This is a promising current area of research and should be expanded.

Following reviewer's comments the authors have expanded the part regarding inhibition of Nf-κB as potential future approach in AP immune therapy including data from Huang et 2013, Yang et al 2012, Sailai et al 2010. Nonetheless, as already stated in this article, data regarding immune-modulation in pancreatitis has been scarce during the last decade in comparison to the past. Ongoing research in the field (strictly limited to immune therapy and not extending to antibiotics, probiotics, proteolytic inhibitors, NO etc) includes observations upon IL-12, IL-22, TNF-a and bacterial translocation, IL-33, HMBG1, mesenchymal stem cell and HLA-DR monitoring already stated in our manuscript

(2) Reviewer 2: In this review, Akinosoglou and Gogos explored the knowledge that has been gathered regarding the role of immune-modulating therapy in acute pancreatitis. The authors evaluate the various inflammatory modulators within an inflammatory setting further complicated by sepsis and consider the feasibility of clinical implementation. This is an interesting review which provides useful information. The manuscript is

nicely written, and it can be accepted for publication after minor corrections. The following points should be addressed:

1. The grammar and spelling has to be revised. E.g. In the Abstract where it says “intensive case” it should be “intensive care”.

Grammar and spelling is now revised

2. These references should be included: In relation to TNF-alpha, together with references 26-29 and 106-110, the authors should include ‘World J Gastroenterol. 2010;16(44):5565-81’.

Reference now added

3. In relation to inflammation NF-kB and trypsinogen activation together with reference 30, the authors should include ‘Gastroenterology. 2011;141(6):2210-2217’.

Reference now added

4. In Figure 1: The paragraph stating “Trypsinogen activation is mediated by intracellular Ca++ signaling and ROS, leading to NF-kB up-regulation”, has to be rewritten according to the Introduction, Local and Systemic Inflammation (page 4): “NF-κB and trypsinogen activation … may be unrelated and both contribute to inflammation, possible through Reactive O2 Species (ROS) mediation and calcium (Ca++) signaling.”

The discrepancy has now been corrected

(3) Reviewer 3: The review is too long and too confusing. Better shorten it and concentrate in the main points regarding every cytokine

The authors thank the reviewer for his comment. However, in view of other reviewers’ positive comments as well as, absence of similar advice, authors would welcome more specific comments upon confusing or redundant parts so that they proceed in further editing. Nonetheless an effort of shortening the text has been made.

(4) Reviewer 4: This is a very well written and balanced review of the evidence/arguments for targeting the immune system as an alternative therapeutic approach in the management of severe acute pancreatitis. The authors have done a very good job of synthesising available information in a succinct manner with a well considered commentary on the pitfalls and challenges in this field, particularly with respect to translating experimental findings to the clinical situation. Specific comments :

1. A cell that has received increasing attention recently in terms of its function in the normal pancreas is the pancreatic stellate cell. Recent studies have provided interesting evidence to support a role for PSCs in innate immunity [Masamune A et al K. J Gastroenterol (2008) 43: 352-62; Shimizu, K et al Pancreas (2012) 41: 422-7.] For the sake of completeness, this issue could be included in the introductory section.

The authors agree that PSC play a role in immune response, even though the recent article by Shimizu, K et al (2012) challenges their contribution in adaptive immunity. However, for the sake of brevity and clarity, the authors have deliberately avoided to give any mention to pancreatic stellate cell here. The reason for this is that most data place PSC activation much later in the time course of pancreatitis .PSC activation is mostly related with recurrent pancreatic injury and chronic inflammation or pancreatic cancer and not acute pancreatitis (upon which this review focuses) (Omary MB, et al. J Clin Invest 2007;117:50–59, Apte et al Gastroenterology. 2013 Jun;144(6):1210-9) .

2. Reference has been made to the autophagic process and IL22. Given that autophagy and UPR are now increasingly recognised mechanisms mediating acinar injury, it would be useful to expand the discussion re

autophagy and its role in immune modulation.
Interesting point. The authors recognise the important role of autophagy in immune regulation and vice versa. A small discussion including data from Clarke et al 2012, Kroemer et al 2010, Saitoh, et al 2010, Levine et al 2011, Deretic et al 2013 has now been implemented in the text accordingly.

3. Where discrepant findings are reported with treatment eg with human recombinant IL-1ra (ref 133 vs 134) and lexipafant (ref 165 and 166 vs 167), it would help the reader if the authors attempted to discuss the possible reasons for such discrepancies.

Possible reasons for discrepancies between trials have already been discussed in the "fiction" section, in an effort to avoid redundant discussions in each immune-therapeutic agent. Nonetheless, a small note for each has now been implemented to facilitate the reader.

Minor points : Page 18, paragraph 1 "….trials of anti-inflammatory therapy has been difficult…." should read "….trials of anti-inflammatory therapy have been difficult…." Page 18, paragraph 1 "This data challenges…." should read "These data challenge…." Page 19, paragraph 2 "…intervention and there is the need of using……" should read "…intervention and there is a need for using……". You may consider adding pancreatic stellate cells to the schema in Figure 1.

Minor points corrected where appropriate. As far as stellate cells please refer to reply to comment 1

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Peter Laszlo LAKATOS, MD, PhD
1st Dept. of Medicine
Semmelweis University
Budapest, Koranyi 2A
H-1083-Hungary
Fax: +36-1-313-0250
E-mail: kislakpet@bell.sote.hu