MAYO CLINIC

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January 26, 2014

Dear Dr Huan-Huan Zhai,

Please find enclosed the edited manuscript in PDF format (file name: 6889-review.PDF). As per the requests of reviewers 1 and 2, we have reduced the length of the inflammatory cell overview section. However, we feel that the nature of the review article (bringing together the fields of inflammatory responses and pancreatic disease) necessitates at least a brief overview of both these topics in order for readers to understand this review of what is known about the complex relationship that exists between the two systems.

Title: A complex role for the immune system in initiation and progression of pancreatic cancer

Author: Kristin S. Inman **(note change in first author's last name)**, Amanda A. Francis, and Nicole R. Murray

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6889

The manuscript has been improved according to the suggestions of reviewers. A highlighted version is provided to indicate changes in response to reviewers' comments.

Reviewer 1:

(1) The manuscript format has been updated to include page numbers and line numbers.

(2) The abstract is now included in the manuscript as well as other components of the "topic highlights" format.

(3) All abbreviations within the manuscript are now defined the first time they are used, and replicate definitions have been deleted. A list of abbreviations is now provided as a separate document.

(4) In response to the reviewer's comment that the first part of the manuscript is essentially the text from an Immunology textbook and could be deleted, we have made the following changes. First, Figure 1 was replaced as suggested. While we did not eliminate the first section of the manuscript, the immune system overview was shortened and refocused on the functions of the immune cells that mediate their roles in pancreatic disease. We retained this section because we feel that although readers with a strong immunology background may find this section unnecessary, readers with a primary background in pancreatic cancer may need this background in order to fully appreciate the subsequent discussion of the role of individual immune cell types in the development and maintenance of pancreatic cancer. Therefore, we have balanced the background to allow all readers, regardless of background, to benefit from this current review of the literature regarding the interaction of the immune system and pancreatic epithelium in the initiation and progression of pancreatic disease.

(5) The reviewer further comments that this review should provide information on the pancreas function, and the consequences of pancreatitis and pancreatic cancer on pancreas function. We thank the reviewer for this comment and have added a brief description of pancreas function, as well as a description of clinical signs, clinical and pathological outcomes, and common treatments and their relative efficacy, as they relate to the diseases we discuss (pages 7-8).

(6) We thank the reviewer for the suggestion to discuss the potential limitations of rodent models in the study of the relation between the immune system and pancreatic cancer. We now include a brief discussion of differences in the immune system and immune environment between humans and rodent models and discuss the limitations of data gathered in rodent models (page 8). We also emphasize the importance of complimentary data from clinical studies and now include additional correlative data from analysis of patient tissue.

(7) The reviewer suggests that we present, in table form, all of the components of the immune system and their products; that are thought to play a role in development of pancreatic adenocarcinoma, with reference to the basis of their suggested role. We thank the reviewer for this helpful suggestion and we have included the suggested information in the form of two tables. Table 1 describes the function of the innate immune cells as it pertains to the normal immune response and the response to cancer, and Table 2 lists the cytokines described in the text as playing a role in pancreatic disease along with their source and target cells.

(8) The reviewer recommended that we prepare an additional figure to present schematically all of the immune mechanisms and pancreatic alterations at various steps in the pathological processes that impact disease development and progression. We thank the reviewer for this comment and agree that inclusion of a figure outlining the interactions of the immune cells with the pancreatic tissue will benefit the reader's understanding of this complex process and effectively summarize the conclusions of this review. This is now included as "Figure 6". We have also included a figure that demonstrates schematically the major cytokines released by the damaged pancreas and the immune cells impacted by these cytokines (Figure 3).

(9) The minor points raised by reviewer 1 have been addressed in the formatting changes and assignment of abbreviations, described above.

(10) Reviewer 1's last minor point "this is an incomplete statement, because T-lymphocytes have a similar role i"… was cut off in the version we received. The reviewer appears to be saying that T lymphocytes also play a role in the body's long-term pathogen-specific response. We have now altered this statement to more clearly indicate that B-lymphocytes are one of the immune cell populations responsible for the body's long-term pathogen-specific response (page 6).

Reviewer 2

(1) The reviewer requests that we cut the description of the immune system, acute and chronic pancreatitis. We agree with the suggestion to decrease the description of basic immune system components, and in response to both reviewers 1 and 2, we have reduced the general description of the immune system. While we did not eliminate the descriptions of acute and chronic pancreatitis, we have refocused these sections, while adding information regarding the pathological and clinical nature of these diseases or order to better show the relevance of the role of the immune system in the development and progression of pancreatitis.

(2) "…increase content of role of the immune cells in PDAC." In response to both reviewers 1 and 2, we have enhanced our discussion of the literature regarding the functional roles of immune cells in the development and maintenance of pancreatic cancer.

Reviewer 3

(1) The reviewer is correct in pointing out that it is generally accepted that in vivo carcinogenesis and progression of cancer is associated with interactions with the immune system. In the revised submission, we have responded to the reviewer's request by emphasizing the mechanisms of interaction between the immune system and neoplastic cells that have been characterized in pancreatic cancer or are unique to pancreatic cancer.

(2) The reviewer suggests that the role of the immune system in initiating pancreatic epithelial cell metaplasia, and it's interaction with pancreatic cancer stem cells should be mentioned in this review. We thank the reviewer for pointing out our oversight. We now mention the recently characterized roles of the immune system in promoting acinar-to-ductal metaplasia (page 15) and in supporting the cancer stem cell phenotype (pages 17-18).

(3) We thank the reviewer for the helpful suggestion that the cellular functions and cytokine cascades by which the immune cells interact with, and regulate the progression of, neoplastic pancreatic tissue, should be represented schematically in the manuscript. We have taken this suggestion and now present a schematic representation of the interplay between the various immune cells and the neoplastic pancreas in the development of cancer (**Figure 3)**. We have

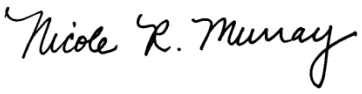
also added a table of the components of the immune system with references to support their suggested role in development of pancreatic adenocarcinoma (Table 1).

Reviewer 4

We thank the reviewer for the positive review of the submitted manuscript.

We thank all of the reviewers for the insightful comments. We have incorporated these suggestions into the revised manuscript, and in doing so, have produced a much stronger and more comprehensive review of the role of the immune system in the development and maintenance of pancreatic cancer. We look forward to publishing this review in the ***World Journal of Gastroenterology***.

Sincerely,



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