

ANSWERING REVIEWERS

September 9th 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4361-review.doc).

Title: FIBROGENESIS AND FIBROSIS IN INFLAMMATORY BOWEL DISEASES: GOOD AND BAD SIDE OF SAME COIN?

Author: Mariabeatrice Principi, Floriana Giorgio, Giuseppe Losurdo, Viviana Neve, Antonella Contaldo, Alfredo Di Leo, Enzo Ierardi

Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 4361

The manuscript has been improved according to the suggestions of reviewers: **reviewer's suggested correction are written in red font while linguistic correction are reported in blue font.**

1 Format has been updated

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

Reviewer n. 1

The review article of Principi et al. entitled "Fibrogenesis in IBD..." is about an interesting topic, but there are some points that needs revision. Regarding bFGF the authors mention that it is a key regulator of collagen fibrosis in both CD and UC. However, the main characteristics of fibrosis in CD is different from the one in UC. What are the known/suspected major regulatory pathways that may be responsible for these differences? If fibrogenesis is a "two-faced" mechanism, what cytokine/chemokine/cellular factors may regulate the bFGF/syndecan system that makes the fibrogenetic process stricturizing in CD, while not stricturizing in UC?

The main difference in the fibrogenesis between UC and CD is represented by the involvement of muscularis layer in the last condition. The concept has been detailed on page 4 of revised manuscript.

A wider review of the regulation of fibrogenesis in CD and in UC would enhance the strenght of the manuscript. At least the role of TGF-beta must be discussed.

A dedicated section was enclosed in revised manuscript in order to detail the different mechanisms of the regulation of fibrogenesis and a large part of this section was focused on TGF beta role.

English language needs minor polishing. After major revision I suggest to accept the review for publication in WJGP.

Language review was performed by a native speaker.

Reviewer n. 2

I read with great interest the Review Article entitled "FIBROGENESIS IN INFLAMMATORY BOWEL DISEASES: A "TWO-FACED" APPEARING RELATIONSHIP"", by Principi et al. The Review is well done, timely and interesting. However, the main drawback is the presence of several orthographical and grammatical errors limits its readability and scientific potential.

Language review was performed by a native speaker.

In particular, Title: It reflects the content of the manuscript and is sufficiently attractive.

The title was modified according to the objection of another referee and corrected as suggested by linguistic reviewer in order to obtain a better agreement with what reported in the text of revised manuscript.

Abstract: It is concise, sufficiently complete and well resumes the entire Review. Keywords: All the reported keywords correctly represent the main field of investigation of the manuscript.

Introductory remarks: This section is well written, although the amendment of some orthographical and grammatical errors might improve its readability. I suggest the substitution of the term "Introductory Remarks" with "Introduction".

Suggested correction has been performed.

Final remarks: This Section although too short is appropriate.

Some sentences have been enclosed in this section of revised manuscript.

References: All of the cited references are appropriate.

Reviewer n. 3

The title does not mirror the experience of the Authors. The conclusions should be more impressive.

The title was modified according to the objection and corrected as suggested by linguistic reviewer in order to obtain a better agreement with what reported in the text of revised manuscript. Further sentences have been enclosed in this section of revised manuscript.

Reviewer n. 4

This minireview deals with fibrogenesis in inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Based on their personal experience, on the behavior of TNF-alpha, syndecan 1, and bFGF, the authors describe a possible molecular pattern for mucosal healing and the implications of its deregulation in the fibrotic complication of Crohn's disease. This paper does not sufficiently addresses recent advances on the pathogenesis, epidemiology, diagnosis and therapy of inflammatory bowel diseases. The analysis of the role of TNF-alpha, syndecan 1, and bFGF is poor and based only on authors' observation on anti-TNF alpha treatment. The results of the pattern of TNF alpha, syndecan 1 and bFGF in patients with Crohn's disease complicated by fibrotic stenosis undergoing surgical resection, described only in a short report (an abstract?), appear to be contradictory and the conclusions are speculative.

Our personal experience is based on four published papers (references 10, 14, 68, 71) as well as in a single abstract (reference 69) whose data have been reported in a paper which is actually under

review. However, the concepts of our personal data are better detailed in revised manuscript and contradictions and speculative conclusions have been avoided according to the suggestions.

Moreover, the implication of other molecular mechanisms, such as adipokines (Endokrynol Pol. 2013;64(3):226-231), JAK/STAT signaling (Pharmacol Res. 2013 Jul 2;76C:1-8), epigenetic mechanisms (Gastroenterology. 2013 Aug;145(2):293-308).

A dedicated section was enclosed in revised manuscript in order to detail the different mechanisms of the regulation of fibrogenesis and a large part of this section was focused on TGF beta, adipokines, JAK/STAT and epigenetic mechanism possible role.

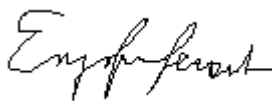
In complex this minireview does not seem to bring new ideas or mechanisms to recently published manuscripts. In summary, I find the opportunity of this review questionable.

We hope that the large revision of the manuscript according to a very accurate review may have been significantly improved the manuscript in consideration that a "minireview" target is to obtain a suitable mixing of literature and personal experiences.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Enzo Ierardi', with a stylized, cursive script.

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