

June 9, 2016.

Prof. Hugh Freeman

Editor-in-chief, Journal of World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 26175

Manuscript title: An overview of cytokines and nitric oxide involvement in immunopathogenesis of Inflammatory Bowel Disease.

Authors: Imene Soufli, Ryma Toumi, Hayet Rafa, and Chafia Touil-Boukoffa

Dear Professor,

Thank you for your invitation to publish in your journal dated May 12, 2016. Here, we submit a revised version of an invited review. The latter has been reviewed after submission in World Journal of Gastroenterology. Our review has been modified accordingly to the remarks and comments of the editorial staff and the reviewers of World Journal of Gastroenterology. We accommodated all of them and this significantly improved the quality of our manuscript.

We hope that you will find this revised version of our manuscript acceptable for publication in World Journal of Gastrointestinal Pharmacology and Therapeutics.

Please, find below the answers for the reviewer's comments.

Sincerely,

Prof. Chafia Touil-Boukoffa

Reviewer 1:

This review gives a comprehensive description of the relationship between cytokines and nitric oxide in immuno-pathogenesis of IBD. However, this article did not explain why in Ulcerative colitis and Th-2 type immune response show the same positive correlation between the pro-inflammatory cytokines and iNOS. The role and mechanism of immunoregulatory and anti-inflammatory cytokines was not be described.

Answer:

This has been added in the text. Actually, we have cited our study showing the presence of Th 17 response in both Ulcerative colitis and Crohn's disease. This study showed also a positive correlation between Th17 cytokines and nitric oxide

production in UC and CD. Also, besides the predominant Th2 response, there are also pro-inflammatory cytokines in UC. Moreover, the defect of the epithelial barrier is considered as a main feature in UC, this leads to bacteria invasion and intestinal inflammation. In fact, the expression of the inducible Nitric Oxyde Synthase is not only induced by proinflammatory cytokines but also by bacterial components such as LPS.

Reviewer 2:

This is well-written review on the role of nitric oxide and pro-inflammatory cytokines and the relation between them in inflammatory bowel disease. only some minor points should be considered: - The manuscript doesn't have abstract. Please include it to manuscript. - Some abbreviations should be brought in complete form at the first appearance in the text. This rule did not observe for some abbreviations such as NF-kB, TNF-a, IFN-gamma, IL-6, IL-1b, LPS.

Answer:

The abstract has been added to the text. The abbreviations are brought in complete form at the first appearance.