

July 15, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3593-review.doc).

**Title: Synergistic effect of interleukin-10-receptor variants in a case of early-onset ulcerative colitis**

**Author:** Martina Galatola, Erasmo Miele, Caterina Strisciuglio, Lorella Paparo, Daniela Rega, Paolo Delrio, Francesca Duraturo, Massimo Martinelli, Giovanni Battista Rossi, Annamaria Staiano, Paola Izzo\*, Marina De Rosa\*

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 3593

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 and the "American Journal Expert" revision.

(1) *There are some confuses in using the terms "inflammatory bowel disease" and "ulcerative colitis". The authors should properly use both terms, respectively.*

We agree with the Reviewer that there are some confusion in using the terms "inflammatory bowel disease" and "ulcerative colitis" and we have revised all manuscript using "inflammatory bowel disease" only related to both diseases, Crohn disease (CD) and ulcerative colitis (UC).

(2) *There are some minor misspellings.*

Manuscript has been revised for language misspelling from "American Journal Expert" as declared in the attached certification.

(3) *Discussion: "According to our hypothesis, we found TNFRI down-expression and TNFRII and IL-10RB over-expression in primary fibroblasts incubated with mesalazine and azathioprine, both in the IBD and in FAP patients. In IBD patient only, azathioprine, but not mesalazine induces a TNFa decrease." Further explain the significance of TNFRI down-expression and TNFRII and IL-10RB over-expression in primary fibroblasts in ulcerative colitis*

We have taken into consideration the Reviewer's point and have upgraded the part of the text in which we discuss the significance of TNFRI down-expression and TNFRII and IL-10RB over-expression expression in ulcerative colitis.

**Discussion. Page 14, line 23**

.....These observation could suggest that these drugs are only able to partially restore IL10 pathway function in UC, by activation of IL10RB, but not IL10RA transcription. On the other hand, down expression of TNFRI and over-expression of TNFRII, could increase risk of colorectal cancer associated colitis in UC patients. As described by Chang et al. [27]., TNFRI has tumour suppressor activity in context of colitis associated cancer and the role of TNFRII, in cell proliferation, is well known

**References. Page 20, line 20.**

We cited Chang et al. (Chang F, Lacey MR, Bouljihad M, Höner Zu Bentrup K, Fortgang IS. Tumor necrosis factor receptor 1 functions as a tumor suppressor. *Am J Physiol Gastrointest Liver Physiol* 2012; 302(2): G195-206.) in the sentence reported above with number 27 instead of 40. All references from 27 to 40 were scaled up of one number.

(4) *Conclusion: "In addition, we suggest that  $\beta$ -catenin and TNFRI protein expressions could represent molecular markers of sub-clinical disease in apparently healthy relatives of patients." Discuss the relationship between  $\beta$ -catenin and TNFRI protein expressions in ulcerative colitis.*

We have discussed the relationship between  $\beta$ -catenin and TNFRI protein expressions in ulcerative colitis, as request from the Reviewer.

**Conclusion. Page 15, line 3**

.....Recent finding suggests that chronic inflammation in IL10<sup>-/-</sup> mice increased P-b-catenin<sup>552</sup> expression, moreover TNFRI exerts its tumour suppressor activity by modulating activation of b-catenin and controlling epithelial proliferation<sup>[43]</sup>. It clearly appear that classical therapeutic approach doesn't look adequate for the IBD patients carrier IL10 pathway alterations because down-expression of TNFRI signaling would confer increased risk of developing colitis associated-carcinoma.

**References. Page 22, line 7.**

We added Lee et al. (Lee G, Goretsky T, Managlia E, et al. Phosphoinositide 3-kinase signaling mediates beta-catenin activation in intestinal epithelial stem and progenitor cells in colitis. *Gastroenterology* 2010; 139(3): 869-81. 881.e1-9.) in the references section with number 43.

According to suggestions included in the article, we also have:

- a) revised the manuscript according to the suggestions of the "American Journal Expert";
- b) revised the format of authorship, as indicated in the format for brief article;
- c) provided PubMed citation numbers for the reference list, e.g. PMID and DOI;
- d) provided the decomposable figure of Fiugres, whose parts are movable, as ppt format.

3 References and typesetting were corrected

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

Sincerely yours,  
Marina De Rosa



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