

November 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5887-review.docx).

Title: Inflammation and colorectal cancer, when microbiota-host mutualism breaks

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5887

We are honored that the reviewers appreciated our manuscript, and grateful for all the precious suggestions strategic to further improve our work. The present version of the manuscript has been ameliorated according to all the points raised by the Reviewer 00058387:

191: the authors mention APC and CTNNB1 as driver mutations in CRC development. It is now appreciated that in contrast to spontaneous CRC development, colitis associated cancer (CAC) is characterized by late mutations in APC. Given the interplay between NF- κ B and Wnt signaling in IECs (Schwitalla et al., Cell 2013), and the inherent pro-survival/proliferation effect of NF- κ B activation, microbiota induced NF- κ B activation in IECs may bypass the requirement of early mutations causing hyperactive Wnt signaling during colorectal cancer development.

In agreement with the Reviewer's suggestion, in the present version of the manuscript the interplay between NF- κ B and Wnt signaling is discussed (page 11, lines 319-321).

At multiple sites in the review, the authors describe changes in microbiota in CRC patients, or specifically at cancerous mucosa compared to healthy mucosa. Could the authors elaborate briefly on the mechanism by which cancerous epithelium can harbor specific bacteria. How can the tumor create a specific microbial niche? (difference in epithelial adhesion, reduced mucin/anti-microbial peptide production at tumor sites,...?). How could passengers show competitive advantage in the tumor microenvironment?

We are sorry for missing this point in the previous version of the manuscript. Possible mechanisms by which cancerous epithelium may select from bacterial drivers are now discussed (page 9, lines 276-278).

In chapter 4 the authors suggest different mechanisms involved in microbial CRC promotion. When discussing the role of inflammation and NF- κ B, it is worth stressing the cell type specific function of NF- κ B in IECs (anti-apoptotic) versus myeloid cells (pro-inflammatory). In this respect, the landmark paper of Greten et al., Cell 2004 is very informative. It is also worth mentioning a few important tumor promoting inflammatory cytokines, like IL6 and TNF.

We are grateful to the Reviewer for raising this point. In the present version of the manuscript the experiments performed by Greten et al., Cell 2004, are mentioned (page 11, lines 312-318).

The authors mention a few examples of TLR and colorectal cancer, but do not mention the importance of inflammasomes. Mice deficient for inflammasome components (casp1, nlrp3, nlrp6,...) have increased susceptibility to CRC development (largely due to lack of IL18). Inflammasome dysfunction also causes dysbioses, which contributes to CRC sensitivity (transmissible!) via epithelial IL6 signalling. Therefore I believe inflammasomes should be discussed briefly in this chapter.

We thank the Reviewer for raising this point we missed in the previous version of our manuscript. The role for a compromised inflammasome function in microbiota-dependent CRC onset is now discussed (page 7, lines 198-200).

365: explain what the abbreviation ATM stands for

The acronym has been explained (page 13, lines 375-376).

370: change (REF) with appropriate reference

We are sorry for the oversight. The appropriate reference has been added (page 13, line 380; Reference 119).

378 and 382, psk+ should be pks+

The correction has been made (page 13, lines 389 and 393).

380: typo: has been recently proven

The correction has been made (page 13, line 391).

408 ...innate immune adaptor Rip1-Rip2. Rip1 and Rip2 are not adaptor proteins but kinases, which act in distinct signaling pathways

The sentence has been rephrased (page 14, lines 417-419).

427 maybe consider to refer to Tbet instead of TBX21 (less frequently used)

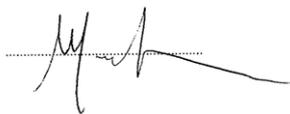
The correction has been made (page 15, line 436).

463 quotation mark missing "beneficial"

The quotation mark has been added (page 16, line 472).

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

Sincerely yours,



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