

Padova, the 28th January 2014

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Title: Inflammatory colonic carcinogenesis: a review on pathogenesis and on immunosurveillance mechanisms

Dear Editor Wen and dear Prof. Ma,

we are submitting the revised version of our manuscript entitled " Inflammatory colonic carcinogenesis: a review on pathogenesis and on immunosurveillance mechanisms" for possible publication in your journal. We are really grateful for the opportunity of improving our work and we hope to have satisfactorily answered to all questions.

We also add to the paper and to the point by pint reply a copy of our previous review written in 2010 and published in 2011 in Annali di Chirurgia just to disclose any possible previous publication on the same topic. Some of the information are obviously the same (it is the same topic!) but the whole body of the review is changed and several information are the most up to date. Please let us know if there is any problem.

Thank you for your kind consideration,
Yours sincerely

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Point by point reply:

Reviewer 1

1. English language should be checked and corrected by a native speaker.
 - We had it checked and corrected by a native speaker
2. The manuscript is rather dense.
 - We organized the paper in subchapters as suggested
3. A couple of figures demonstrating the different pathways leading to cancerization and at least one figure for the evolution of the cancer would be advisable.
 - We included also three figures to make the take home message easier to grasp

Reviewer 2

The review “Inflammatory colonic carcinogenesis: a review on pathogenesis and on immunosurveillance mechanisms” by Scarpa et al. is a well written review on clinical data concerning pathologic mechanisms in ulcerative colitis- promoted colorectal cancer (CRC). The review covers genetic aspects such as genomic instability and DNA damage, the role of onco-suppressor genes and apoptosis pathways, and inflammation related enzymes such as Cox-2 and iNOS. One chapter is dedicated to the role of immunosurveillance in inflammation-driven CRC mainly covering the role of CD4+ Tcells. The authors also include own views and opinions within the review. There are some suggestions that may improve the quality of the paper:

1. The manuscript is organized in three chapters. For a reader it may be much easier if the main points of the chapters can be shown in a figure. The review only contains text, figures would help to grasp the essentials quicker.
 - We included also three figures to make the take home message easier to grasp
2. In general, there is a long body of text that could be better organized in sub-chapters and paragraphs to make the reading easier
 - We organized the paper in subchapters as suggested
3. Mainly literature concerning ulcerative colitis is included but not much about Crohn’s disease and CRC. If it was only intended to cover the topic of UC then this should be highlighted in the abstract. Otherwise some information on Crohn and CRC should be included.
 - We focused this review on ulcerative colitis so we consequently highlighted it in the title and in the text.
4. The role of pro-oncogenic cytokines and transcription factors in inflammation-driven colon cancer is only little covered. It would be good to include a small paragraph that addresses this interesting topic in more detail.
 - We added a dedicated subchapter addressing this point