RESPONSE TO REVIEWERS

MANUSCRIPT ID : 39281

Reviewer – 1 (ID: 00227487)

I think this review article is well written and comprehensive. However, following two reviews can be cited. 1) Tanaka T. Colorectal carcinogenesis: Review of human and experimental animal studies. J Carcinog. 2009;8:5. PubMed PMID: 19332896 2) Rosenberg DW, Giardina C, Tanaka T. Mouse models for the study of colon carcinogenesis. Carcinogenesis. 2009 Feb;30(2):183-96. PubMed PMID: 19037092

Response : We thank this reviewer for the suggestion. As per the advice of this reviewer, we have incorporated the two references in the manuscript (References No.34 and 155)

Reviewer – 2 (ID : 00183445)

The manuscript meets the main criteria for publication. The work contains important epidemiological data on the prevalence of colorectal carcinogenesis. It classifies polyps and indicates the possibility of their transformation and focuses on the role of inflammatory response in colorectal carcinogenesis. Describes symptoms, risk factors and stages of colon cancer. A significant advantage of the work is the presentation of the best experimental models of colorectal cancer. The Authors discuss the role of epithelial cells as target cells in colorectal cancer. Emphasizes the importance of various types of cell death to search for new therapeutic tools. Finally, signaling pathways in colon cancer are well described as a tools for new terapeutic options. The article is well constructed. It requires only a few language corrections, especially in the use of commas. Figure 2 needs to clarify the abbreviations. I am not convinced about the pictures inside Figure 3. It is better to make a table. In general it is a good proposition among medical review articles.

Response : We thank this reviewer for evaluating this review. We apologize for not abbreviating the contents of the figure. Fig.2 and Fig.3 was completely modified in

this revision. A schematic representation of major cell death pathway has been incorporated in this revision. Please refer to figures 2 and 3.

Reviewer – 3 (ID: 02440884)

The review is focussed on pathways driving colorectal carcinogenesis. In the manuscript important pathways are mentioned and some networks are addressed. Comments 1. Important pathways should be illustrated with detailed schemes. 2. The molecular network of the different pathways should be addressed in detail. 3. miRNAs are important players in CRC. They should be introduced to the reader. 4. The serrated pathway and MSI pathway should be given.

Response : We thank this reviewer for the expertise. In this revision, we have included the schemes of important pathways (Figures 4-6). We have also added the miRNA as a separate section. However, due to page constrains and length of the manuscript, we couldn't address the molecular network of the different pathways.

Reviewer – 4 (ID : 00073640)

The title is topical and the abstract is promising. The manuscript is well written and structured. However, there are some major drawbacks that need to be corrected: 1. Section Colon polyps – gate keeper in CRC: the whole section needs to be properly corrected, including the title. Gate keeper in CRC???? In this section data and definitions are oversimplified and do not represent the actual pathological knowledge. Colon polyps are macroscopically visible pathological formation, protruding above the mucosa surface into colon lumen. Histologicaly, polyp can represent a mucosal fold, inflammatory formation, benign (hyperplastic, dysplatic lesion, adenoma) and malignant tumor (carcinoma). Cautiously, the term polyp denotes also other formations!!! Colon polyps are not the lesions with aberrant growth that appear on the colon. There are also various forms of flat lesions and dysplatic crypts (they are not polyps) that can progress in CRC. CRC can also arise from carcinoma in situ, which is not polyp. When there is a talk about polyps, hyperplatic, adenomatous or malignant lesions, which are terms that denote precise pathology, there is a need to be correct and not to mislead. Therefore, I strongly suggest including correct pathological definitions and classification in this section. 2. Section- Symptoms and risk factors: Authors wrote: "The risk due to environmental factors include consuming diet rich in red meat and fat, etc...". It

was found that the composition of the fat in more important than the amount of ingested fat. For instance, diets high in n-3 polyunsaturated fatty acids (PUFA), olive oil or n-9 monosaturated fatty acids have shown a protective or no effect on the colon carcinogenesis in animal models, while diet high in saturated fatty acids, such as lard or beef tallow, and n-6 PUFA, such as corn or sunflower oil, has been associated with an increased risk of colon cancer. 3. Section - Stages of colon cancer: Figure 1 is misleading and does not show all stages correctly – stage III and IV includes the whole organism. It is also interesting that authors did not picture polyp structure (described in the previous section), but only small lesion inside the mucosa. 4. Murine models of colorectal cancer: murine models are briefly introduced, therefore I strongly suggest refering the readers to some good review articles of particular model for more information about characteristics of a model. 5. Section Epithelial cells: Authors wrote: "The abnormal accumulation of epithelial cells can cause mutation in oncogenes and tumour suppressor genes that result in polyp, the neoplastic growth." Delete the word polyp from the sentence (as explained under point 1). "Thus formed adenomatous polyps in the colon and rectum, which is a benign lesion, have the potential to further develop into cancer and metastasize to other organs" Replace the word polyp with the term lesion (see point 1). 6. Currently, there are different signaling pathways known in CRC – for instance, hereditary CRC (FAP, hereditary nonpolyposis), sporadic CRC (serrated, non-serrated), CRC associated with ulcerative colitis. In the article not all pathways are mentioned. Thus, I suggest introducing all currently known pathways otherwise the authors should reform the title (sporadic CRC for instance). 7. Schematic presentations of signaling pathways would additionaly improve the manuscript.

Response: We thank this reviewer for spending the valuable time to work this manuscript. The critics raised by this reviewer are genuine and worth to discuss. We agree with the comments of the reviewer. As per the suggestion of this reviewer, we have discussed the colon polyps. The symptoms and risk factors were rephrased. The figure of stages of colon cancer is improved to the possible extent and murine models were elaborated. The schematic representation of signaling pathways is incorporated in this revision.

Overall response to the reviewers

We thank all the reviewers for their time to strengthen this manuscript. We regret for those minor typographical errors and some erroneous sentences that reduces the enthusiasm of reading. In this revision, we have incorporated additional figures and also improved the quality of figures. Apart from these, we have added new section (miRNA, Murine models & Delta notch pathway) to strengthen this manuscript. This revision is now comparatively much more elaborate than the previous one. I request you to review this again and give your suggestion. We will be glad to incorporate any additional corrections as per your advice. We thank the Editorial team as well as the reviewers for evaluating this review.