To
The Editor,
World Journal of Gastroenterology

Dear Editor,

We have carried out a number of revisions to the manuscript titled "Eicosanoid pathway in colorectal cancer: recent updates" (Manuscript number: 19001) by Sinem Tunçer and Sreeparna Banerjee.

The language of the manuscript was described as "Grade B". As I am a native speaker of English and therefore consider my scientific English to be of a high standard, I request a re-evaluation of the quality of the language by the Editor. The reviewers have also commented the manuscript to be 'well written' and 'well-conducted and appropriately written'. I have included a statement (uploaded to the Journal website) where I take responsibility for the quality of the language.

Other suggestions made by the editor (such as spacing before the reference number and decomposition of the figures) have been carried out in the revised manuscript. The decomposable images as powerpoint files have also been uploaded.

All the comments made by the reviewers have been addressed in a point by point manner below. All changes made to the manuscript have been annotated by 'Track Changes'. A version of the manuscript where the 'Track Changes' have been 'accepted' is also included.

Kind regards,

Sreeparna Banerjee

Response to Reviewers comments

REVIEWER 1

- The manuscript is excessively long; it can be shortened because this is a limitation for readability of the study, but it is not a fatal flaw.

  Response: We have shortened the manuscript by removing paragraphs that did not directly relate to colorectal cancer (CRC). We have also removed the paragraphs pertaining to the epoxygenase pathway, restricting the manuscript instead to the COX and

LOX pathways that are studied more in the context of CRC. The corresponding references that were included in the deleted paragraphs have also been removed.

- Purpose of the study was stated, it was inadequate. But it should have purpose and objectives stated.

  Response: The purpose of the study was to highlight the latest literature on the importance of bioactive lipids in CRC, while at the same time emphasizing on the fact that these lipids may have opposing roles in the process of neoplastic transformation.

  For this we have amended some sentences in the abstract as follows:

  "In this review we have evaluated the cancer promoting and anti-cancer roles of different eicosanoids in colorectal cancer, highlighting the latest literature on the effects of these molecules not only in the tumor tissues, but also in the tumor microenvironment. We have thereby attempted to delineate the roles that these opposing bioactive lipids play in neoplastic transformation in CRC through effects on proliferation, apoptosis, motility and metastasis and angiogenesis."

- In the conclusions section; the "so what?" question has not been answered adequately.
- It should be emphasized what it has been adding to the literature already known and what new contribution this new information has been making to the practice.

  Response: We thank the reviewer for these comments. We have added several sentences to the Conclusions section where we have discussed what is lacking in the field and what the future prospects look like. These sentences have been appended below:

  "There is no doubt that eicosanoids are an important family of immunoregulatory bioactive lipids with strong implications for both promotion and prevention of colon cancer. During inflammation, many of these autacoids act antagonistically or synergistically; frequently in a temporal manner involving different cell types in order to bring about homeostasis. Many of these bioactive lipids are also essential for various cellular functions. Despite its importance, very few therapeutic options are available that can modulate the aberrant production of these molecules specifically in the context of colorectal or other cancers. ASA is undoubtedly one of the best known drugs that can interfere with the COX pathway; however, ASA needs to be consumed long term (at least 5 years) in order to observe any protection from cancer. Use of ASA is also associated with significant bleeding events and is thus not suitable universally. COX-2 inhibitors, that specifically target the inflammatory arm of the COX metabolism pathway, are approved primarily for pain relief rather than for cancer chemotherapy and are also

associated with significant cardiovascular side effects. CysLTR antagonists were designed for asthma, yet have not had widespread proven efficacy[208]. Since inhibition of one pathway leads to the activation of another due to the shunting of the substrates, combined COX/LOX inhibitors have proved to be more efficacious and need to be explored further in the context of CRC.

The identification of a 'druggable' target in the generation of eicosanoids is necessary, with a concerted effort from the scientific community to develop drugs that are specifically effective in cancer. Perhaps the greatest promise comes from the newly discovered resolution mediators such as lipoxins, resolvins and mareisins; early studies indicate that these mediators are effective at very low concentrations. Therefore, the efficacy of these compounds as viable chemopreventive/therapeutic options in CRC may be anticipated.

It is also interesting to note that COX-2 or 5-LOX that are associated with pro-carcinogenic events or 15LOX-1, which is associated with anti-carcinogenic events in CRC, rarely show any mutations. Deregulation in their activity comes from their overexpression, enhanced enzymatic activity or silencing. Therefore one may envisage the design and development of chromatin modifiers that can reduce the expression of the pro-inflammatory enzymes such as COX-2 or 5-LOX while enhancing the expression of the anti-inflammatory enzymes such as 15-LOX-1.

There is no dearth of information in the literature and clinical trials highlighting the importance of eicosanoids in cancer. Delving into the details of how the eicosanoids function both in the tumor as well as in the stromal cells will be essential to understand the pathways involved, which will, in turn aid in the design of novel cancer therapies."

- The references (at the end of the text and in the text) should be reorganized in terms of the number and citation in the text. For example, you can see little mistakes in the text. The number of references can be reduced.

  Response: We have removed a considerable amount of text from the manuscript and all the references that were cited in those sentences. The manuscript was checked in detail for typographical and other mistakes.

REVIEWER 2

This is a well written account of eicosanoid pathway in colorectal cancer. However, the contents may be too wide-ranging, and lose focus. Thus the reviewer suggests that the manuscript should be shortened, concentrating on colorectal cancer.

Response: We have removed several paragraphs from the text that did not directly relate to colorectal cancer. We have also removed the paragraphs on the epoxygenase pathway, thereby restricting the discussions to the COX and LOX pathways. The manuscript therefore now has been considerably shortened and edited.