Dear editor:

Thank you very much for giving the opportunity to revise our manuscript, we have checked the manuscript, provided the point-to-point answers to editors and reviewers, and made revisions in the context accordingly.

Sincerely yours,

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Response to Editor Comments:

Reviewer 1

Comment : Interesting review. It would have been better had the authors discussed relationship between genetic and epigenetic events in the pathobiology of inflammation induced colon cancer.

RE: Many thanks for your suggestion. This article focuses on the role of epigenetics in the transformation of inflammatory cancer. Based on your opinion, we have drawn four figures and two tables based on the content of each subheading to further explain how epigenetic modifications regulate genes in the pathobiology of inflammation induced colon cancer.

Reviewer 2

Comment : 1-This review needs tables for each subheading, and figures to explain schematically the action of the different etiology mechanisms conceptually leading from inflammation to cancer development.

RE: Thanks for your suggestion. I completely agree with your opinion. Based on your opinion, we have added four figures and two tables based on the content of subheading.

to further explain schematically the action of the different etiology mechanisms conceptually leading from inflammation to cancer development.

2-The action of chronic administration of anti-inflammatory drugs in reducing the prevalence of colorectal cancer should be reported in a separate sub heading., adding a meta analysis which shows the results of the several prospective studies which have demonstrated the reduced prevalence of colorectal cancer in patients taking anti-inflammatory therapy.

3-The role of inflammation in colorectal cancer development opens many new therapeutic horizons, including the role of new anti-inflammatory drugs. The Authors should add a sub-heading on this possibility. In this context, the Authors should analyze the possible side-effects, including the possibility of increased mortality and morbidity in head trauma, which national statistics have shown increased in the last years in the lederly (probably related to the action of anti aggregant-anti inflammatory chronic administration in the elderly).

RE 2 and 3: Thanks for your suggestion. We have added a subtitle for anti-inflammatory drugs and CRC. This section mainly introduces the benefits and side effects of anti-inflammatory drugs in the treatment of CRC. Please refer to the "ANTI-INFLAMMATORY AGENTS AND CRC" section for details.

4-I would freccomend to give special attention to the relationship of mucionous adenocarcinoma and inflammation. In patients with inflammatory bowel disease, there is a higher prevalenece of mucinous secreting adenocarcinoma, which is not evident in sporadic and familiar cases.

RE: Many thanks. I think the relationship between mucinous adenocarcinoma and inflammation is a very interesting topic, indicating that the development of inflammatory bowel diseases to CRC has its special mechanism. There is very little literature on the content of research in this area. I will continue to pay attention to this aspect of research in the future.

5-Colorectal cancer etiology implies many genetic factors. Inflammation seems to play a major role.

RE: I agree with your opinion. This article focuses on the role of epigenetics in the

transformation of inflammatory cancer. Inflammation is now regarded as an enabling characteristic for the acquisition of the core hallmarks of cancer. The release of pro-inflammatory cytokines is involved in the formation of immune microenvironment for the occurrence of CRC.

6-Among the many actions analyzed in the review, the Authors should include the increased production of inflammatory cytokines and growth factors which are present in the inflammatory cascade. The sub heading should also include the specific role of NK-f and the canonical and not canonical activation of this factor.

RE: Thanks for your suggestion. The NF-κB and STAT3 signaling pathways play a particularly important role in the transformation of inflammation into CRC. Based on your comments, we have further explained the role of NF-κB signaling pathway and the activation pathway in the introduction section of the article. The details are as follows: "The NF-κB signaling pathway includes both classical and non-canonical pathways. The classical pathway is activated by pro-inflammatory cytokines, pathogen-associated or damage-associated molecular patterns. The non-canonical pathway is activated by a small subset of cytokines including lymphotoxin, receptor activator of NF-κB ligand, CD40 ligand and B cell activating factor of the TNF family. Activation of NF-κB not only affects DNA damage and carcinogenic mutations, but also causes tumorigenesis by promoting the production of reactive oxygen species and reactive nitrogen. It can also cause chromosomal instability, aneuploidy and epigenetic changes, leading to tumorigenesis and development."

Reviewer 3

Comment : The idea and concept of this review is excellent and clinically important. Cancer and inflammatory diseases have been classified as non-communicable diseases for decades. Both diseases have characteristics of immune reactions, which are principally identical, but differing in important aspects. Still, the idea of connections between cancer and inflammation is often overlooked. The authors adequately introduced the situation and subsequently methodically went through individual epigenetic factors. All were substantially discussed. The paper is

well-referenced and I am sure that it will serve as a excellent source of information on this subject.

RE: I am especially grateful for your recognition of my article.

Reviewer 4

Comment: This review is well written and summarized for the chronic inflammation-induced epigenetic changing-mediated CRC. If the authors could add the solution as well the future perspective for it, it will be more informative and helpful for readers.

RE: Many thanks for your suggestion. We have added a statement about the future perspective. The details are as follows:……"An in-depth understanding of this process will allow us to clarify the pathogenesis of CRC, and some epigenetic modifications can be used as markers for CRC diagnosis." …… "For example, DNA demethylation promotes tumor suppressor genes expression to re-establishing tumor prevention, and reducing expression of pro-inflammatory cytokines by regulation of histone modifications or ncRNAs, ultimately reduces inflammation infiltration of tumor microenvironment. In the future, this new anti-tumor drug may be used in combination with immunotherapy, chemotherapy and targeted cancer therapy for the treatment of CRC. Role of epigenetics in the transformation of inflammation into colorectal cancer were explored which may help stimulate futures studies on the role of molecular therapy in CRC."