

Response to the Reviewer's Comments and Suggestions

We sincerely thank the reviewer's for their time and effort in reviewing this review article and mostly positive review. We also thank the reviewers for their concerns and constructive suggestions. We have revised the original article as per reviewer's suggestions and hope that the revised article is considered suitable for publication. The major changes in the article have been colored blue for clarity.

Reviewer#1

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The role of MSCs in therapy of Inflammatory Bowel Disease is a very actual problem in regenerative medicine. The manuscript is very informative and of a good quality, but has several little drawbacks:

1. Source No. 3 "cdc, c., Data and Statistics. 2019" is not indicated correctly. Could you please give more precise reference?

Response: We have included more precise reference in the revised article.

2. Title "Where do we stand: Current knowledge of the disease prevalence and pathobiology?" was formulated as a question. I believe that either all the titles should be phrased in the form of questions, or it is worth reformulating the title of this chapter (not as a question).

Response: We have revised the article as per reviewer's suggestions.

3. In the part "... and believed to promote disease severity, relapse, and its progression to neoplastic transformation and growth [6, 10]." you could also mention colorectal cancer.

Response: Thanks for the suggestion. We have included the suggestion in the revised article.

4. In the sentence "Notably, almost 100 trillion bacteria commensally inhabit the GI tract of a normal human [13]." please make a link to the source.

Response: The suggestion has been incorporated in the revised article.

5. "A number of factors which are suspected to promote IBD include polymorphisms in genes like NOD2 / CARD15 [21, 27], CCR6, ICOSLG, JAK2 / STAT3, FIT2, PTPN2, ATG16L1, NRP3, CARD9, IRGM1 and a few others [25, 26]. " Is it possible to reduce the number of given genes?

Response: We have shortened the list of the genes in the revised article.

6. You mention monozygotic twins, but in my opinion this is not quite correct. Since IBM is a multifactorial disease, it cannot be argued that this disease in twins is caused uniquely by a genetic predisposition.

Response: We agree with the reviewer's point of view and wanted to underscore this point by using the example of the monozygotic twins. Their data itself reflect roles of both genetic predisposition as well as of environmental factors.

7. In the "potent contributory factor in individuals of early age groups" part, you should specify the age group you mean.

Response: Reviewer suggestion has been incorporated in the revised article.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: This review titled "Inflammatory Bowel Disease: Therapeutic Limitations and Prospective of the Stem Cell Therapy" does not fit its content, as much of the review focuses on Anti-IBD therapies: current status and potential challenges. There are few keywords. The table is very disorganized, in some parts it gives the reference from where the information was obtained, but not in all. The table refers to therapies without stem cell involvement. The conclusions and future directions are focused on stem cell therapy and the figures have good quality and they are appropriately illustrative of the paper contents. Concerns:

1-Table 1 must be re-written and add a specific column to place the references where the described information is found.

Response: Table-1 has been revised to for clarity and readability.

2-It would be very useful if the authors made a table with the stem cell therapies that are being tested in animals and those that have already made the leap to the clinic on an experimental basis.

Response: We thanks the reviewer for this suggestion, however do not believe that the current data in this area is streamlined enough to create a succinate table in an informative manner.

3-Please, check on page 6 if Reference 20 is really describing that individual's gut microbiota is shaped not only by the genetic predisposition but also by environmental factors including diet, exposure to the antibiotics, physical activity and financial status.

Response: We have checked the authenticity of the reference for the stated functions.

4-Total words of main document is missing.

Response: We have included this information in revised article.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The review by Rangnath Mishra and coll. gives an interesting update on inflammatory bowel diseases and stem cells. Title, abstract and keywords are adequate for the manuscript subject. The background clearly describes the state of the art and the problem and, more in general, the review is very exhaustive and clear, maybe just a little too long, being in some points prolix. In general, the review is quite original and it underlines the potential role of stem cells for the treatment of bowel diseases. My only suggestion is to try to shorten some paragraph (such as "The underlying mechanisms..."), to make the text more readable. Figures and tables are very useful and they help the reader.

Response: We thanks the reviewer for the encouraging and constructive review. Reviewer's suggestions have been taken into account in the article revision.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an important article about inflammatory bowel disease. The conclusion may be revised to clarify the major therapeutic approach to treat the disease more in detail. Proofreading is needed.

Response: We have revised the conclusion and done careful proofreading of the revised article.