

Round 1

Dear Editor,

We sincerely appreciate your consideration and giving us the opportunity to revise the manuscript. Comments from the reviewers and Science Editor are invaluable and we have given equal importance to all the comments. Based on the comments we have made a major revision of the manuscript and I am also responding to all the comments in the text below. We are providing the revised manuscript with MS word Track changes as the main text file.

Reviewer: 1

Reviewer's Comment: The review has given a detailed review about role and mechanism of CXCR4-SDF1-HMGB1 axis in directional migration of cells and regeneration of injured tissues. The structure of the paper is clear and illustrated. Review is rigorous and conclusion is credible according to total induction and description.

Authors' Response: Thank you very much for reviewing our manuscript and giving encouraging comments.

Reviewer: 2

Reviewer's Comment: In this review manuscript, the authors plan to describe the role of HMGB1-SDF1-CXCR4 pathway in the migration of cells for tissue regeneration. However, there is nothing new can be obtained by the readers and the summary and the discussion are not in-depth. I suggest the authors should focus on the regeneration of one specific tissue with few cell types and then discuss the role of HMGB1-SDF1-CXCR4 pathway.

Authors' Response: Thank you very much for reviewing our manuscript and giving thoughtful suggestions. We agree that there are plenty of articles on the individual components of this pathway and the axis itself in regulating the migration of cells. However, the articles on this axis contributed very little in the field of regenerative medicine. Hence, in this manuscript we have attempted to explain the role of this axis on the directional migration of cells needed for the regeneration of affected organs (in general). In future when we will write a manuscript on the effect of this axis in the regeneration of a targeted tissue or organ, we will follow your precious suggestions. Thanks again for your constructive comments.

Reviewer: 3

Reviewer's Comment: Comments to the authors The manuscript by N. Haque et al., entitled "Role of CXCR4-SDF1-HMGB1 Pathway on the Directional Migration of Cells and Regeneration of Affected Organ" describes the pathways of elicited by HMGB1-SDF1-

CXCR4 which orchestrate migration of cells toward the injured tissues and the role of different types of cells involved in regeneration. So far, the bulk of information regarding regeneration has been focused on stem cells, but proper consideration of the role of stromal cell-derived factor-1, SDF1, in migration of the cells needed for regeneration is still scarce. In this sense the present article covers an important and required issue. In particular, the authors gave attention to the not very well-known roles of the protein non-histone nuclear protein, HMGB1, in orchestrating the process of migration and regeneration. Also, the authors provided a description of the mechanisms of action of many paracrine factors released by transplanted stem cells and emphasized on the role of activation of SDF1-CXCR4 or HMGB1-SDF1-CXCR4 pathway during migration and retention of the transplanted cells. In addition, the manuscript reviewed the role of many cell types, including Mesenchymal stem cells, among others, in regeneration and, very importantly, the authors described how MSCs interact with their microenvironments to modulate regeneration during inflammation and tissue injury. Finally, the schematic diagram, included as Fig 1, about the role of HMGB1–CXCL12–SDF1 axis in regenerative processes clarify many of the concepts explained in the text. The manuscript is well written, and it gathered many of the currently available references. Up to now one the major problems faced to use stem cells in the clinic is to control migration and retention of transplanted cells. So, the manuscript is important and necessary to enlighten our knowledge about this critical medical problem. Minor point Authors please check carefully all the abbreviations used need to be explained when used for the first time in the article

Authors' Response: Thank you very much for reviewing our manuscript and giving inspiring comments. We appreciate your effort to find out the merit of this manuscript. It obviously will encourage us to do better work in future. We have checked all the abbreviations carefully and provided elaborations where needed. Moreover, changes are marked in red.

Science Editor:

Issue raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Authors' Response: Thank you very much for giving us the chance to submit the revised version of this manuscript. We were able to find one grant approval letter. Hence, we are providing necessary document for that. Acknowledgement to another grant has been removed.

Issue raised: (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Authors' Response: The figure is prepared using PowerPoint and the file is provided.

Issue raised: (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Authors' Response: We have revised the references carefully. All the authors' names are provided in the references. Duplicated references are removed. PMID and DOI numbers are added. For the references numbered 1, 15, 40, 69 and 111, we were not able to provide PMID numbers. Hence, as per journal policy we have provided the first page of these articles as supplementary.

Issue raised: Please revise throughout.

Authors' Response: We have revised the manuscript thoroughly. The manuscript was revised with MS word Track changes.

Sincerely yours,

Nazmul Haque, Ph.D.

Faculty of Dentistry

MAHSA University

Malaysia

Round 2

Dear Editor, We sincerely appreciate your consideration and giving us the opportunity to submit supporting documents related to the manuscript. Comments from the reviewers and Science Editor are invaluable and we have given equal importance to all the comments. I am responding to all the comments in the text below.

Reviewer: 1 Reviewer's Comment: The authors have made the required changes. The manuscript is interesting and valuable.

Authors' Response: Thank you very much for reviewing our manuscript and giving thoughtful suggestions that helped to improve its readability.

Reviewer: 2 Reviewer's Comment: No comments.

Authors' Response: Thank you very much for reviewing our manuscript.

Science Editor: Comment 1: Please revise the manuscript according to the 2nd review report. Please provide point to point answer to all reviewers. Authors should revise their article according to the reviewers' comments/suggestions and provide point-by-point responses to each in a letter that is to accompany their resubmission.

Authors' Response: Further corrections were not requested by the reviewers. Hence, any revision is not done.

Comment 2: Audio core tip: Please offer the audio core tip, the requirement are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications: Acceptable file formats: .mp3, .wav, or .aiff Maximum file size: 10 MB

Authors' Response: As per your suggestion an audio core tip has been prepared in MP3 format and submitted accordingly.

Comment 3: Please provide the Copyright License Agreement signed by all authors.

Authors' Response: Copyright License Agreement signed by all authors has been provided. We were able to upload only one file (Audio core tip) using the provided space. Please let me know how can I send the copyright transfer form to you. If you need further information please let me know. Thank you very much for your kind support. Sincerely yours, Nazmul Haque, Ph.D. Faculty of Dentistry MAHSA University Malaysia