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Manucript type: REVIEW

Micromanaging cardiac regeneration: Targeted delivery of micrnas for cardiac repair and regeneration

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Answers to Reviewer (ID: 00744036)

Comments to authors:

Review of Micromanaging Cardiac Regeneration: Targeted delivery of MicroRNAs for Cardiac Repair and Regeneration (ESPS Manuscript NO: 21847) This article covers the roles of miRNAs in heart disease for regenerating cardiomyocytes and its different modes of delivery. Overall, it is a precise and well documented review paper. However, after through reading, I would like to make following comments.

1. English proficiency in the article is not very good. There are numerous typos and grammatical mistakes. I would like to suggest that the authors ask a native English speaker to edit the manuscript. Some mistakes are as follows.

a. Page 5, paragraph 2, line 10: Please inert "in" after "improved".

b. Page 5, paragraph 2, line 19: Please consider revising this part of the sentence: "and chronic heart failure is to likely develop"

A: this sentence has been changed in : At this stage, chronic heart failure is likely to develop as the cardiac tissue is unable to regain its normal function.

c. Page 10, paragraph 1, line 4: Please omit "in their ability" from the sentence.

d. Page 10, paragraph 1, line 6: Please remove "into" after cardiac fibroblasts.

e. Page 12, paragraph 2, line 8: Please insert "were" after "microRNA-ome"

f. Page 12, paragraph 2, line 10: Please consider revising the following sentence. "MicroRNAs that are highly regulated (increased or decreased) in ESC-derived cardiomyocytes compared to native ESC and that were not regulated in cardiac fibroblasts were identified as cardiomyogenic microRNAs or "cardiomiRs".

A: this sentence has been changed in: MicroRNAs that are differentially expressed in ESC-derived cardiomyocytes and native ESC and that are not expressed by cardiac fibroblasts were identified as cardiomyogenic microRNAs or “cardiomiRs”.

g. Page 14, paragraph 2, line 19: Please replace “increased” with “increase”.

h. Page 14, paragraph 2, line 22: Please remove “and” after “liposomes”.

i. Page 23, paragraph 2, line 12: Please insert “is” after “processes”.

A: the above listed textual changes have been made to and are highlighted in the manuscript. Furthermore, the manuscript has been proofed by Dr. J.K. Burgess, a native English speaker.

2. Please give space before starting new paragraphs, as per the formatting requirements of the journal.

A: The space prior to a new paragraph has been inserted in the revised manuscript file in accordance to the formatting requirements of the journal.

4. Please briefly describe the biogenesis of microRNA.

A: We acknowledge the reviewer for pointing out this omission and have added a brief description of microRNA biogenesis to the beginning of section 2.3 (page 11, starting at line 21).

5. Please mention the advantages and disadvantages of RNA-based therapeutics for cardiovascular disease compared with conventional drug approaches.

A: We agree with the reviewer that a reference to current treatments for cardiac failure add to the value of this perspective. However, currently there are no therapeutic options in the clinic that induce cardiac regeneration. We have added this statement to our introduction on page 5, starting at line 21. Furthermore, experimental approaches to induce cardiac regeneration (either pre-clinical or in clinical trials), such as growth factor therapy (page 6), stem cell therapy (page 6-8) and fibroblast reprogramming using genetic viruses (page 9-11) are already discussed in this perspective as it the advantage that microRNA-based therapies may have over them.

6. Please add a paragraph that briefly describes the miRNA target genes in cardiovascular disease.

A: The reviewer puts forth an interesting question, however highly ambiguous. There are >100 microRNAs described in human cardiovascular disease (>50 in cardiac disease alone) that combined target over a 1000 genes. Describing these would result in a review that is, in our opinion, outside the scope of this perspective. Hence, we have decided to focus solely on microRNAs that are involved in cardiac (re)generation and their experimentally validated target genes. These are described in detail in section 2.3 of our manuscript and illustrated in figure 2.

7. Reference section: The first author name should be in bold style, as per the journal formatting



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requirements. If the above changes are made. I would like to recommend this review paper for publication.

A: We have adjusted the reference style in accordance to the journals formatting requirement

Answers to Reviewer (ID: 00608588)

Comments to authors:

This is a very important and well written review.

Response to reviewer:

We thank the reviewer for his/her kind assessment of our manuscript and the compliments.