

Answer to reviewers

Stem cell-derived exosomes – an emerging tool for myocardial regeneration

Reviewer #1:

Thank you for your analysis and for your appreciation regarding the novelty of our manuscript. Following your pertinent observations, we have made the below mentioned corrections to our manuscript. All the changes are highlighted in the text.

Observation no. 1: *The manuscript by Lazar et al. discusses the potential role of exosomes as theranostic tools for myocardial regeneration. This is a topic undergoing intense study and interest at the present time, but the editing of manuscript needs to be revised. The punctuation of sentence or paragraph is not clear that may cause reading difficulty; English is to be further polished. A careful editing is needed to correct spelling mistakes, for example on page 2, abstract, line 6, and respectively page 3, paragraph 2, line 7 "may attempts....." should be read as "many attempts....."; also, "beneficial" is repeatedly written as "benefical" (e.g page 2 abstract, page 3 paragraph 4, page 5 paragraph 8). Other examples of frequent misspelling are: "indward" instead of "inward" and "apaptosomes" instead of "apoptosomes".*

Answer no.1: Thank you very much for this positive appreciation! We had the manuscript edited by a native English speaker and all the errors and misspellings have been corrected in the text.

Observation no. 2:

Since the theme of the paper is "Stem cell-derived exosomes – an emerging tool for myocardial regeneration", I suggest the authors should expand a little more the section "Exosomes as myocardial regenerative tools".

Answer no.2: Thank you for the valuable observation, we agree with it. Subsequently further details were added about the role and possible use of exosomes in myocardial regeneration after myocardial infarction and this section of the review was extended. Further, the role of exosomes in myocardial regeneration is also addressed in the subheading "exosomes and cardioprotection" a.

Observation no. 3: *In addition, I think the impact of manuscript would be improved if authors would address the challenges related to isolating high yields of pure exosomes from plasma/serum and from cells cultures.*

Answer no.3: Thank you for this remark, we agree with it and added a subtitle called "Isolation and purification of exosomes" with a brief detailing of isolation and purification methods of exosomes.

Reviewer #2:

Thank you for your appreciation regarding our manuscript and also for the suggestions to improve it. We realize the importance of including your suggestions in the text and we made the necessary adjustments.

Observation no. 1: *The main message of the paper is not clear enough. The author should clarify the extent of impact that exosomes may have in stem cell therapy in humans. They have not concluded that failed stem cell therapy so far will be resolved by employment of exosomes or we are not at the level to judge right now. I think it is a question to be clearly addressed.*

Answer no.1: Thank you for this important suggestion. We believe that exosomes might represent the future of regenerative cardiovascular medicine, which may overcome the limitation of stem cell therapy. We reformulated the conclusions to clarify this issue and highlighted the fact that further studies are needed to make a final statement on exosome therapeutic options.

Observation no. 2: *There is potential for redundancy all around the text. Core tip is almost the same as abstract and abstract is most similar to the introduction. I recommend rephrasing the core tip emphasizing on two important messages of the review which are emergent role of exosomes as therapeutic agents and diagnostic biomarkers. this is true for titles so that it is evident from the titles that they talk two times on "role of exosomes in myocardial regeneration".*

Answer no.2: We agree with this remark and we reviewed the core tip and corrected it, emphasizing the potential role of exosomes as a biomarker and therapeutic option in myocardial regeneration.

Observation no. 3: *Moreover, there is significant overlap between ACS and MI so that these two entities could be discussed in the same or two following sections. I highly recommend forming a list of contents and merging similar topics to make the text appear more integrated.*

Answer no.3: Thank you for this recommendation, we agree with it, subsequently the structure of the review has been revisited and parts with similar topics have been merged. “Exosomes in acute coronary syndromes” has been revised and renamed “Exosomes and atherosclerosis, including consideration on exosomes and plaque vulnerability, while the parts addressing regenerative therapies post myocardial infarction have been merged in the last heading. At the same time, “exosomes in injured hearts” has been replaced by “exosomes in CVD” and limited to potential application as biomarkers, therapies and nanocarriers, in order to avoid overlap with regenerative applications.

Observation no. 4: *The review is claimed to be focused on exosomes' role; However, there are ambiguities in some parts for instance when they talk about exosomes as biomarkers the*

reader is confused whether or not and exosome could be served as biomarker as all section is about the role of MiRNA which is included in exosome.

Answer no.4: Thank you for your observation, we agree with it. As exosomes are sources of miRNA, which can be detected in various cardiovascular diseases, serving as a valuable biomarker, we considered that it is important to discuss this issue in the manuscript. To avoid confusion in the readers we renamed the subtitle “Exosomes as disease biomarkers and diagnostic tools” to “Exosomes as source of biomarkers in cardiovascular diseases”.

Observation no. 5: *My proposal is giving brief explanation on terms such as Killip score which is not familiar to readers who are not cardiologist.*

Answer no.5: Thank you for this suggestion, we agree with it and a brief explanation of Killip classification was added to the mentioned paragraph.

Observation no. 6: *The English writing needs some polishing and probably more important is meticulous review of the text by authors to correct many mistakes caused by rapid preparation of the text.*

Answer no.6: We had the manuscript edited by a native English speaker and all the errors and misspellings have been corrected in the text. The English native speaker is now a co-author of the manuscript, also having a significant contribution to the review process.

We would like to thank the reviewers for the time allocated to improve this review!!