Peer Review File

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Reviewer A:

Sihan Liu et al, in their review manuscript entitled, "N6-adenosine methylation (m6A) RNA modification in the pathophysiology of heart failure" discusses the role of m6A RNA methylation in heart diseases. M6A mRNA methylation, a conserved and abundant post-transcription modification, is established in the eukaryotes. Recent studies have shown its role in the progress of cardiovascular disease and heart failure. This review has proper headings and subheadings. This review summarized the available information and suggested its importance in heart failure. The following suggestions may enhance the quality and readability of this review article:

1. Line 32: The data presented for heart failure is a bit old. Please update with recent heart failure data of the USA and its burden (AHA has released this data last year).

Reply 1: We have updated the related pandemic data of heart failure with and we have cited the latest reference of related data.

Changes in the text: See page 2 line 19-20

2. Line 68: The adequate information regarding the writer is missing. I will suggest to add a proper writer complex information and to extend the discussion in more detail as RNA methylases are the key components of methylation machinery.

Reply 2: We have written the relative information of m6A writer. Since the limit of the size of text, more detailed information would make this review too long,making it hard to meet the journal's requirement.

3. Line 70: Inclusion of details and comparative analysis of ALKBH5 and FTO will enhance the strength of this article.

Reply 3: We have searched the related article focusing on the difference between ALKBH5 and FTO. However, the current studies focus on the mechanism difference of the two molecule and those mechanisms were rarely related to heart failure. Thus, it's difficult to add related information.

4. Add the importance of ALKBH5 and its role in angiogenesis post-Ischemia, (doi.org/10.3389/fcvm.2021.817304) will extend the information in the study.

Reply 4: We have cited the required literature in the text

Change in the text : Page 14 line 19-22

This is a significant topic. However, this article is developed on pre-existing reviews with limited novelty. So I guess, the impact will be low.

Reviewer B:

The manuscript by Liu et al. reviewing the recent studies of the RNA N6-adenosine methylation role in

pathophysiology of heart failure. This is very important, interesting, and highly relevant for translational science topic. In order manuscript to be acceptable for publication the authors should address several comments:
- A list of abbreviations should be included in order to facilitate the reading.

Reply 1: We have made an abbreviation list. See in the supplymentary material.

- The paragraph "Biological function of m6A" should be shortened and more focused on the main mechanisms. The figure is explanatory enough.

Reply 2: We have shorten the requested part.

- Figure 1 has several typos that should be corrected.

Reply 3: We have made correction

- A figure demonstrating the main mechanisms of m6A related to the pathological processes in the heart should be included.

Reply4:We have draw a figure demonstrating the main mechanisms of m6A related to the pathological processes. See figure 2.

- A language proofreading and typos corrections is mandatory.

Reply5: We have made proof reading.

Reviewer C:
In this manuscript, Liu et al. review current information on the role of m6A RNA modification in heart failure. In general, the review is timely, as the interest in epigenetic modifications that contribute to heart failure are growing and the focus on m6A RNA modification is of great interest. The manuscript is thorough though the inclusion of some additional content is suggested (see below).

Specific Comments
1. Though Figure 1 is helpful, the inclusion of an additional table that summarizes all of the Reader, Writer and Eraser proteins regulating m6A would be helpful. As written, the section is fairly dense and a table will help to quickly index the proteins mentioned.

2. The organization of the m6A effects on pathology is reasonable, though it would have been nice to see a section dedicated specifically to ischemia or ischemia/reperfusion related m6A changes. There are some studies woven throughout, but a dedicated section would be beneficial for a reader interested in this specific topic.

Reply2: We have added the related paragraph as requested.

4. Are there studies evaluating m6A changes in the diabetic heart? Because the diabetic heart, left untreated, can ultimately go into failure, the inclusion of this information would be beneficial in its own section.

Reply3: Since the relative article is rare, we made discussion in future perspective part.

4. The Future Perspectives section is somewhat underwhelming. First, the entire first paragraph is unnecessary, as it does not directly address the topic of future perspectives. This paragraph should be removed from the section. Also, there are not a lot of future directions provided. I think this is a missed opportunity for the Authors, as this topic is relatively new and fresh. As a result, a review likes this can be very beneficial to the research community and the future perspectives section is where this is perhaps most important. I would suggest that the Authors think a little more about what is needed in terms of research moving forward for this field and include those ideas in this section. Without doing so, the impact of the manuscript will be greatly lessened.

Reply4: We have made the correction in discussion part.

5. There are some grammatical errors that should be addressed. A good proofread is advised.

Reply5: We have sent our article to edited by a language editing company.