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Manuscript title: Epigenetic basis of Alzheimer disease

56749-Answering Reviewers

We thank the reviewer for his/her comments, observations, and recommendations, which were very useful to improve our manuscript. We have marked in red color the changes performed in the manuscript.

Reviewer #1:

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: This is a mini review paper dealing with association between epigenetic changes and occurrence of AD and aging. The following points should be taken into account prior to publication of this paper:

1. On page 2, the statement regarding the elimination mechanism of β-amyloid peptide should be re-written to make it clear.

Authors response: As the reviewer suggested, the elimination mechanism of beta-amyloid peptide was re-written to make it clearer (page 4, paragraph 3).

2. In the section of DNA methylation in AD, 5-mc should be used instead of 5-methycytosine and 5-hmc instead of 5-hydroxycytosine.

Authors response: Attending the reviewer's suggestion, in this new version, in the section of DNA methylation in AD, 5-mC was used instead of 5-methylcytosine and 5-hmC instead of 5-hydroxymethylcytosine.

3. In the section of histone acetylation and deacetylation in AD, is sodium butyrate a correct HDAC inhibitor?

Author response: Yes, sodium butyrate is an inhibitor for HDACs. Here, we reference some papers:

> Min Jung Park & Farida Sohrabji: The histone deacetylase inhibitor, sodium butyrate, exhibits neuroprotective effects for ischemic stroke in middle-aged female rats. Journal of Neuroinflammation 2016.
>
> James R Davie. Inhibition of Histone Deacetylase Activity by Butyrate. J Nutr 2003.

4. In the section of non-coding RNAs, is “miRNA-125b-1” or miRNA-125b” correct? How about miRNA-206?

Authors response: miRNA-125b-1 and miRNA-125b are correct. It has been reported two precursors of miRNA-125b in humans: miR-125b-1 and -2. These have an identical mature miRNA sequence (miRNA-125b). Thus, mature miRNA-125b can be derived from precursor miR-125b-1 or miR-125b-2 in a cellular type-dependent manner (Yong Sun Lee, et al. JBC 2005).

In this case, miRNA-125b-1, specifically, is reported in neocortex from postmortem AD patients by Pogue AI et al. *(Cellular and molecular neurobiology* 2018), whereas a decreased expression of miR-125b is reported in blood cells by Fransquet PD, et al, (*Clinical biochemistry* 2018).

On the other hand, the miRNA-206 has also been associated with AD. We have added more information about it (page 12, paragraph 2).

5. Several miRNAs such as miRNA193b, miRNA200b, miRNA00C, miRNA29a, miRNA29c are missing in this section. Is “lncRNA-51a” or “lncRNA-51A” correct?

Author response: We thank the reviewer for this observation. lncRNA-51A is the correct. We have performed this correction.

In the section non-coding RNA these miRNAs (miRNA-193b, -200b, -200c, -29a y -29c) are mentioned. So far, it has been reported changes in their expression under AD condition, but their molecular mechanisms remain to be elucidated (page 12, first paragraph).

6. Please also check Figures 2 and 3. All the RNA expressions should be the same.

Author response: The reviewer is correct. We thank the reviewer for this observation. In this version, we have performed the corrections in the RNA expressions in Figures 2 and 3.

7. In this paper there are so many biomarkers which can be used as indicators of AD progression. Which biomarker can be more reliable? The authors should comment on this score.

Author response: As requested by the reviewer, we have commented about which can be the biomarkers more reliable in the non-coding RNAs section (page 12, paragraph 2).

8. The conclusion section can be shortened to make it more concise. Only significant findings can be included.

Author response: As requested by the reviewer, in this new version of our manuscript, the conclusion was shortened to make it more concise.