

December 8, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14739-review.doc).

Title: Epigenetic regulation of stemness maintenance in the neurogenic niches

Author: Montalbán-Loro R, Domingo-Muelas A, Bizy A and Ferrón SR.

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 14739

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer #1:

This manuscript from Montalbán-Loro et al. is an excellent review on epigenetic regulation in neural stem cells. This is a young but growing topic. Such review is thus perfectly relevant and timely. The manuscript is very well written, and the illustrations are of high quality.

We thank the reviewer for his/her positive comments.

I have minor comments for improvements:

- 1. In their Introduction on neural stem cells, the authors cite the manuscript of Encinas et al., 2011 regarding the depletion of the pool of NSCs. I would suggest to mention also an alternative model from Bonaguidi et al., 2011 Cell. It may be worth also citing the “unifying” review from Bonaguidi et al., 2012 Current Opinion in Neurobiology.**

We thank the reviewer for these suggestions. We have added these references in the uploaded version.

- 2. In the legend of Figure 1, (e) is missing and (d) should be (f).**

We thank the reviewer for detecting this typo. We have corrected it in the uploaded version.

- 3. I believe there is an inversion in the arrows in Figure 2. The arrow with DM and HAT should go from top (inaccessible chromatin) to bottom (accessible chromatin) and vice versa for the one with HDAC and DNMT.**

The reviewer is completely right. We have indeed changed the direction of the arrows from inaccessible chromatin to accessible chromatin.

- 4. There is a misspelling in Figure 2: HDCA should be replaced with HDAC.**

We thank the reviewer for detecting this typo. We have corrected it in the uploaded version.

Reviewer #2:

Overall, this is a well-written and highly relevant review. I have just a few minor comments, as follows:

- 1. Intro (p. 3, lines 2-5): There is apparently an odd temporal continuity issue in the statement 'The existence....was first described...(Li and Xie, 2005). Since then....(Altman, 1962)'. The authors may want to check.**

We thank the reviewer for detecting this temporal continuity issue. We have now corrected it in the uploaded version.

- 2. Where Figures are referred to, in the text, they should indicate the relative sub-figure (e.g. Figure 1a, 1b, 2c, ecc), rather than be repeated as Figure 1 or Figure 2. Such general indication is more appropriate for the introductory chapters.**

We have indicated the relative sub-figures in the uploaded version.

- 3. A final 'Conclusions' or 'Future Perspectives' chapter would be appropriate**

We thank the reviewer for this suggestion. We have added a "Future Perspectives" chapter.

- 4. There is something missing in the legend for Fig. 1. There are some misspellings in Fig. 2 (Accesible chromatin)**

We have changed it.

Reviewer #3:

This review article tried to update the knowledge about the epigenetic regulation of stem cells in the neurogenic niches, and it covers several epigenetic mechanisms, such as DNA methylation & demethylation, histone modifications (methylation & de-methylation, acetylation & de-acetylation), and genomic imprinting. The authors also discussed the epigenetic changes during neural stem cells reprogramming and their implications for the stemness maintenance.

The major concerns are:

1) This topic has been extensively studied and reviewed and I am not convinced that this review is absolutely necessary or timely.

We agree with the reviewer about the extensive revisions made in some epigenetics aspects, mainly those related to the histone modifications regulating the neurogenesis process; however less is known about the implication of methylation and de-methylation functions in the neurogenic niches and how this processes regulate imprinting in the neural stem cell population.

2) This review summarized the important findings from the epigenetic field related to the mechanisms of stemness maintenance of neural stem cells in the neurogenic niches. However, the layout and the underlying structure of this review seem to be defective in such a way that I can't see the internal logic that combines different parts together, nor the clear conclusions and the future implications of this article.

We very much appreciate the reviewer's comments and suggestions on our manuscript. We have tried to improve the clarity of the text in the revised version and added a "*Future Perspectives*" chapter to include the important future applications and main conclusions of the review.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Sacri R. Ferrón', with a stylized flourish at the end.

Sacri R. Ferrón SR PhD
Departamento de Biología Celular
Universidad de Valencia
46100 Burjassot, Spain
Phone: +34-963 543784 (office) 3246 (lab)
Fax: +34-963 543404
e-mail: sacramento.rodriguez@uv.es