September 23rd, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12770-edited review.doc)

Title: Imprinted Zac1 in Neural Stem Cells

Author: Guillaume Daniel, Udo Schmidt-Edelkraut, Dietmar Spengler, Anke Hoffmann

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 12770-edited

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. All changes are marked in blue font. Language and grammar have been carefully amended.

Reviewer **02446025**

However, in the conclusion, the authors should discuss and give the specific future direction on the role of Zac1 in the diagnosis or treatment of associated conditions ranging from imprinting disorders to age-related diseases.

Answer:

In the conclusion we comment additionally on the role of variation in genomic imprinting in relation to complex phenotypes as a result of environmental exposures and across lifetime. This hypothesis is supported by a number of studies showing altered imprinting patterns during early life following various pre- and postnatal exposures; however, less evidence exists presently for age-related diseases.

Reviewer **0190528**

Although the Ms. is mainly focused in Zac1, the authors also summarize the state-of-the-art of other imprinted genes relevant for the neurogenic process. In this regard, some important imprinted genes known to participate in cell cycle control and neurogenesis are missing from this initial discussion. For instance, Necdin and MAGE-L2 are two imprinted genes present within the Prader-Willi-Syndrome imprinted region which have been shown to be relevant for the differentiation of the nervous system, but they are not mentioned in this review. Another example of imprinted gene expressed by stem cells is Peg3, which should be included in this review.

There are several statements throughout the text that are not supported by references. Just as an example, most of the statements from pages 16 and 19 lacks references. Authors should make an effort to include references for all statements included in the Ms.

Minor points: 1. In page 12, lines 8-9, it is stated that “Zac1 can also act as a coregulator for unrelated transcription factors of the nuclear receptor or p53 family”. Does this imply that nuclear receptor is synonym of the p53 family? 2. Page 14, lines 11-13: the p53 family has also a key role in apoptosis. 3. Page 15, 7-8: “the cornu ammonis layers of the Ammon’s horn” is a redundant expression.

Answer:

We include a new section on the imprinted gene *necdin*, which is part of the *Zac1* imprinting gene network and shares with Zac1 a role in the regulation of cell cycle progression and apoptosis.

As stated in the Core tip and introduction this manuscript aims to highlight – but not to comprehensively review – recent evidences in the scientific literature on the critical role of imprinted genes in NSCs with a major focus on Zac1. In this respect, imprinted genes like *MAGE-L2* or *Peg3* with less characterized roles in NSCs appear beyond the scope of this review.

Additional references have incorporated throughout the manuscript and in particular for the previous pages 16 to19 as proposed by the reviewer.

All minor points raised by the reviewer have been worked over and amended.

3 References and typesetting were corrected

Thank you again for consideration of our manuscript for publication in the *World Journal of Stem Cells*.

Sincerely yours,

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