progress in neurobiology

Peer Review Overview

Manuscript Title: Role of Circular RNAs in Brain Development and CNS Diseases

Received	15-Aug-2019
1st Decision	04-Dec-2019
Revision Submitted	13-Dec-2019
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Decision Letter

Ref.: Ms. No. PRONEU_2019_186
Role of Circular RNAs in Brain Development and CNS Diseases
Progress in Neurobiology

Dear Dr Vemuganti,

Thank you for submitting your manuscript to Progress in Neurobiology. We have received comments from reviewers on your manuscript. Your paper should become acceptable for publication pending suitable minor revision and modification of the article in light of the appended reviewer comments.

When resubmitting your manuscript, please carefully consider all issues mentioned in the reviewers' comments, outline every change made point by point, and provide suitable rebuttals for any comments not addressed.

To submit your revised manuscript go to https://www.editorialmanager.com/proneu/ and log in as an Author where you will see a menu item called 'Submission Needing Revision'.

Please resubmit your manuscript by Feb 02, 2020.

We look forward to receiving your revised manuscript.

Yours sincerely,

Aimee Kao
Associate Editor

Sabine Kastner
Editor-in-Chief
Progress in Neurobiology

Comments from the Editors and Reviewers

Reviewer 1

The present article provides a comprehensive and current review of circular RNA biogenesis and biological activity in brain development and disease. The article is topical, well conceived and well written, is clinically relevant and appropriate for the mission of the Journal. I have only minor suggestions for improvement:

1. If the Journal permits, the article could be improved by inclusion of a Table of Contents, and sub-headings within in the individual chapters.

2. Although the article describes different methodological approaches for quantifying and analyzing circular RNAs, this topic could deserve a separate section for context and ease of reference (see recent article by Pandey et al: Methods for analysis of circular RNAs. Wiley Interdiscip Rev RNA. 2019 Sep 5:e1566.)

3. Readability for Figure 1 could be improved by changing the light green color of the nucleotide marks to a darker color, similar to Figure 2.

4. One clinically-relevant aspect of targeted gene therapy is cell-type specific expression and biological activity of non-coding RNAs. The Authors do include a reference to this (Salzman et al, Cell-type specific features of circular RNA expression. PLoS Genet 9, e1003777.), however this point could be specifically highlighted in the article. This might be most appropriate to discuss in the sub-section on epigenetic modification of circular RNAs.

5. A recent article by Holdt et al (Circular RNAs as Therapeutic Agents and Targets. Front Physiol. 2018 Oct 9;9:1262.) highlights advances and potential challenges in circRNA-based therapies, which would be appropriate for this review.

Author Response Letter

Reviewer 1

If the Journal permits, the article could be improved by inclusion of a Table of Contents, and sub-headings within in the individual chapters.

Response: Per the “Instructions to Authors”, Prog. Neurobiol. format doesn’t include Table of Contents. The journal uses subdivision (numbered sections).

Although the article describes different methodological approaches for quantifying and analyzing circular RNAs, this topic could deserve a separate section for context and ease of reference (see recent article by Pandey et al: Methods for analysis of circular RNAs. Wiley Interdiscip Rev RNA. 2019 Sep 5:e1566.)

Response: We added the description of methods to study the circRNAs in the revised manuscript. Please see page 7. We also added a new Figure (Fig. 2) so that these methods are easily followed.

Readability for Figure 1 could be improved by changing the light green color of the nucleotide marks to a darker color, similar to Figure 2.

Response: We revised Fig. 1 as suggested.

One clinically-relevant aspect of targeted gene therapy is cell-type specific expression and biological activity of non-coding RNAs. The Authors do include a reference to this (Salzman et al, Cell-type specific features of circular RNA expression. PLoS Genet 9, e1003777.), however this point could be specifically highlighted in the article. This might be most appropriate to discuss in the sub-section on epigenetic modification of circular RNAs.

Response: We highlighted the cellular specificity and biological importance of the circRNAs in the revised manuscript. However, at this time, except for the paper we referred (Salzman et al. 2012), there is no other information available regarding the targeted gene therapy in a cell type-specific manner using circRNAs. We discussed this study and indicated the possibility of using cell-specific circRNA expression as a future therapeutic option. There are only a few studies to date that indicated that circRNAs could be epigenetically modified (Wang *et al.*, 2015; Yang *et al.*, 2017; Zhou *et al.*, 2017), which are added in the manuscript.

A recent article by Holdt et al. (Circular RNAs as Therapeutic Agents and Targets. Front Physiol. 2018 Oct 9;9:1262.) highlights advances and potential challenges in circRNA-based therapies, which would be appropriate for this review.

Response: We added a section describing the advances and potential challenges in circRNA-based therapies. Please see page 31 to page 33.

References

Wang, X., Zhao, B.S., Roundtree, I.A., Lu, Z., Han, D., Ma, H., Weng, X., Chen, K., Shi, H., He, C., 2015. N(6)-methyladenosine Modulates Messenger RNA Translation Efficiency. *Cell* 161**,** 1388-1399.

Yang, Y., Fan, X., Mao, M., Song, X., Wu, P., Zhang, Y., Jin, Y., Yang, Y., Chen, L.L., Wang, Y., Wong, C.C., Xiao, X., Wang, Z., 2017. Extensive translation of circular RNAs driven by N(6)-methyladenosine. *Cell Res* 27**,** 626-641.

Zhou, C., Molinie, B., Daneshvar, K., Pondick, J.V., Wang, J., Van Wittenberghe, N., Xing, Y., Giallourakis, C.C., Mullen, A.C., 2017. Genome-Wide Maps of m6A circRNAs Identify Widespread and Cell-Type-Specific Methylation Patterns that Are Distinct from mRNAs. *Cell Rep* 20**,** 2262-2276.