

Format for ANSWERING REVIEWERS

November 05, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14409-review.doc).

Title: Current focus of Stem cell application in retinal repair

Author: Alonso-Alonso ML and Srivastava GK

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 14409

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

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

(1) 1st reviewer comment

I suggest you to add a separate section on proposed routes of administration of these 03 types of stem cells, to make the article interesting to clinicians.

Authors Answers: thanks for your suggestion. We have included following text and table to incorporate your suggestion in the article.

ROUTES OF ADMINISTRATIONS OF THE ESC, THE iPSC AND THE ADMSC.

The present review describes both *in vitro* and *in vivo* studies. In the second one, the researchers have used different routes of administrations of the stem cells for evaluating the safety and efficacy of their approaches. The subretinal space^[10,11,13,16,21,23-25,35] is a place most frequently used to inject the stem cells, but it has been also used the intravitreal^[16,32,43] and intravenous^[6] administrations. Table 2 presents a summary the routes of administration of each type of stem cells discussed in this review.

Table 2. Summary of the routes of administrations of the stem cells

Type of Stem Cells	Route of administration	Species used	Reference
ESC-neural stem cell	Subretinal and intravitreal	Rat	Lu, B.et al. 2013 ^[16]

ESC- retinal progenitor cells	Subretinal space	Mouse	Cui, L et al. 2013 ^[21]
ESC- photoreceptors	Subretinal space	Mouse	Decembrini, S. et al 2014 ^[10] Gonzalez-Cordero A. et al. 2013 ^[11]
ESC-RPE	Subretinal space	Rat	Diniz, B. et al 2013 ^[13]
iPSC	Subretinal space	Rat	Fang, I-M. et al 2013 ^[35]
hiPSC-RPE	Subretinal space	Rat	Kamao, H. et al 2014 ^[24]
		Mouse	Maeda, T et al. 2013 ^[25]
iPSC-photoreceptors	Subretinal space	Pig	Zhou, L. et al. 2011 ^[23]
hiPSC-neural progenitors	Intravitreal	Rat	Satarian, L. et al 2013 ^[32]
ADMSC	Intravitreal	Rat	Haddad-Mashadrizesh, A. et al. 2013 ^[43]
ADMSC	Intravenous	Rat	Yang, Z. et al. 2010 ^[6]

(2) 2nd reviewer comments

The review is interesting and the information could be useful for those who plan to use stem cells to restore the structure and function of the retina.

Authors Answers: thanks for your appraisal and comments

May main concerns are indicated below:

1) The advantages and disadvantages of the different approaches to use stem cells are conveniently summarized through the manuscript; however, an important issue that has not been discussed is the fact that most of these possible therapies are intended to replace retinal cells that disappeared by apoptosis. The authors point out that those treatments using MSCs may be also useful as neuroprotective agents, but other than that, the use of stem cells, would not prevent apoptotic progression (the main cause of these diseases). Therefore, it is important that the authors include a paragraph, in the conclusions, indicating that this is an important and, still, unsolved problem.

Author answers: thanks for your comments. We have improved the conclusion incorporating your suggestion.

In the last few years, there have been important advances in the area of stem cells, which have made feasible their application in the cell replacement. **It could be used** as a cell replacement therapy for the untreatable retinal diseases **where cells could not be recovered due to cell damage.** Besides, a type of the stem cells, the MSCs, are useful as neuroprotective agents, but other than that, the use of stem cells, would not prevent apoptotic progression (the main cause of these diseases) and this is an important and, still, unsolved problem. The advances in the both approaches should be taken into

consideration as realistic therapeutic options for developing treatments for the untreatable retinal diseases. However, previous to apply these advances to clinical therapy, it is necessary to perform extensive investigations to improve the processes of obtaining, differentiation and implantation of these cells to overcome the challenges, which are still present.

2) There are too many spelling and syntax errors. It should be necessary that the authors make a full revision of the text

Authors Answers: the article has been thoroughly checked for the mistakes and they are corrected.

(3) 3rd reviewer comments

However this manuscript is a valuable summary of potential Stem cell application in retinal repair and would be of interest if published, it needs a major revision before the publication process.

Authors Answers: thanks for your appraisal and comments. We have performed revision thoroughly and improved the article incorporating your comments and suggestions along with other fellow reviewers.

The authors should consider to provide the readers with any graphs or photos illustrating those biological mechanisms in order to lift the value of the manuscript.

Authors Answers: Authors do not agree with reviewer suggestion. This review article is based on the approaches used in published articles. It does not describe in details about the biological mechanisms involved in each approach. It only describes the recent advances in research which seem interesting for performing in vivo test, thus, transferring the results to clinic in short period.

Stem cells have also shown the neuroprotective effects on the degenerating retinal cells which could be applicable to delay or stop the cellular damage events, thus, it could be useful to treat the retinal diseases in their early stage. However, this review is mainly focused for the cell replacement therapy which is applicable in late stage of the retinal degeneration diseases. This review article is based on the approaches used in the published articles. It does not describe in details about the biological mechanisms involved in each approach. It only describes the recent advances in research which seem interesting for performing in vivo test, thus, transferring the results to clinic in short period.

The text should be also revised by the native speaker to correct all language and grammar errors that still exist.

Authors Answers: the article has been thoroughly checked for the mistakes and they are corrected.

Finally, perhaps a pedantic point: glaucoma affects retinal ganglion cells and their axons, but “glaucoma” is not a retinal disease, as well as non-arteritic anterior ischemic optic neuropathy. In my opinion the authors should clarify it to the readers.

Authors Answers: thanks to reviewer for suggestion and we have corrected it.

In addition of the AMD^[2-4], currently there are many other retinal diseases, such as retinitis pigmentosa^[4,5], diabetic retinopathy^[4,6], and eye diseases, such as glaucoma and non-arteritic anterior ischemic optic neuropathy, in which there are damage produced on different retinal layers (table 1).

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

Sincerely yours,

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