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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26866

Title: Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes

Reviewer's code: 02446101

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2016-04-29 18:25

Date reviewed: 2016-05-05 18:10

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

In this review, you clearly summarised how MSCs induce Treg and Breg cells to provoke immunosuppression, which sufficiently confirmed that MSCs possess a great potential to treat autoimmune diseases. The manuscript provides the readers some innovative and valuable information. Further studies are expected. So, acceptance should be recommended for this manuscript.



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26866

Title: Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes

Reviewer's code: 02446319

Reviewer's country: South Korea

Science editor: Fang-Fang Ji

Date sent for review: 2016-04-29 18:25

Date reviewed: 2016-05-18 08:48

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

I read your paper, contribute well . mechanisms involved in Treg and Breg cell induction by MSCs , did well to summarize . If you modified a little more modern and comfortable Figure design , it will be even better.



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26866

Title: Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes

Reviewer's code: 02398400

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2016-04-29 18:25

Date reviewed: 2016-05-19 03:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The review by Ma and Chan provides a comprehensive and well-balanced overview of immune effector cell phenotypes and functions, and how MSCs influence the activity of these cells. The authors do a good job of describing cell-based and animal-based studies to support the different proposed mechanisms by which MSC interact with immune effector cells to alter their function. Only a few minor concerns were noted. 1. In the introduction the authors use the phrase “the re-education propensity of MSCs”. This term is misleading as “education” of immune cells is typically associated with antigen presentation and clonal deletion. Therefore, the term “re-education” should be replaced. 2. The authors do a good job of pointing out that PGE2 can be anti and pro-inflammatory. Nevertheless, they paint a picture that proteins secreted by MSCs are always therapeutic. Although few negative studies are published, there have been more than a few MSC-based clinical trials that have failed to meet their primary endpoints. A cautious discussion about potential negative effects of cells is warranted. For example, TGF-β1 is pro-fibrotic and therefore its secretion by MSCs in tissues may promote fibrosis. 3. Similarly, the authors



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describe the genetic engineering of MSCs as a way to overcome inter-population heterogeneity and poor homing *in vivo*. However, the latter topics are not discussed in any detail despite the fact that are critical determinants that limit potency. Also, no description of the inherent risks of genetically modifying cells is provided. These topics should be addressed at least in a cursory manner. 3. The authors state that expressed levels in MSCs of adhesion proteins, such as VCAM1 and ICAM, are low under normal conditions. However, these adhesion molecules are known to play fundamental roles in regulating hematopoiesis and HSC trafficking in bone marrow. These authors should clarify the different roles played by these molecules, and that low levels may not influence immune cell function but do regulate hematopoiesis. 4. The manuscript requires editing for English grammar.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26866

Title: Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes

Reviewer's code: 00503126

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2016-04-29 18:25

Date reviewed: 2016-05-20 01:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

Ma and Chan review mechanisms by which MSCs interact with Treg and Breg cells to modulate immune responses. This is an important area in biomedical research, as multiple centers are pursuing the use of MSCs for clinical use. The paper is a condense, but informative depiction of the field. Some suggestions to improve the manuscript include: 1. Because of the confusion in the Treg field, a recent recommendation was published suggesting a uniform nomenclature (Nature Immunology 14, 307-308 (2013)). It is suggested that the Treg section of this review conform with the published recommendations, wherever possible. 2. In the sentence indicating the "Retroviral viral transfer of FoxP3 to na?ve T cells upregulated the expression of Treg cell-associated genes", it is important to not that FoxP3 only upregulated the expression of a subset of Treg cell-associated genes. 3. In the discussion of Breg cells, there is a statement: "So far, there are several Breg subsets have been identified in mice. They include CD5+CD1dhi B, Tim1+ B cells, and marginal zone B cells". There are subsets within these populations that include Breg cells, but the entire population does not consist of B cells, particularly for MZ B cells. 4. In addition, improvement of grammar and sentence structure



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would assist greatly in the readability of the manuscript.



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

ESPS manuscript NO: 26866

Title: Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes

Reviewer's code: 02446219

Reviewer's country: Iran

Science editor: Fang-Fang Ji

Date sent for review: 2016-04-29 18:25

Date reviewed: 2016-05-31 01:01

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
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<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors have summarized immunomodulatory properties of MSCs. Overall, The review is very well written and at the same time comprehensive. It is very informative to readers working in the field, and very instructive to readers working outside of the field. I regard this manuscript is worth publishing.