

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46087

Title: Characterization and sequencing analysis of inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA

Reviewer's code: 03551035

Reviewer's country: Romania

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-01-29 08:39

Reviewer performed review: 2019-01-30 08:07

Review time: 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Huang et al. discusses the effects of inflammatory cytokines on the morphology and quantity of mesenchymal stem cells exosomes, but more importantly, the differential expression of microRNAs in the exosomes. This subject worth deep

studying, considering its wide clinical application. The article is well written in general, although I have some minor suggestions to be included in the manuscript. 1. A careful editing is needed to correct minor spelling mistakes, for example on page 3 "diseasesl" should be read as "diseases". Frequent repetitions should be also corrected (such as "impact"/ "impacted" on page 3-4). 2. The numbers showing the cell purity (85% to 95%) (page 4) should be displayed under chapter "Results" instead of chapter "Materials & Methods". 3. Chapter "Results" (page 7): the concentration of MSCs-exo in the IL-6 group should be also presented (data showed only for the other 3 groups). 4. Data (including figures) should be presented as "Experimental vs. Control" instead of "Control vs. Experimental" (e.g., "VCAM-1 vs. Control" instead of "Control vs. VCAM-1" and so on....) (Figure 6, 8, 9...). 5. I think that the impact would increase if the authors could show comparatively the number of relative angiogenesis gene distributions in the VCAM-1/ TNF α /IL-6 group into one graph (bars with different color for each group) (Figure 10 a, c, e). 6. I suggest the authors to comment on the similarities and differences with other similar studies in the literature (for instance, Domenis, Rossana, et al. "Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes." Scientific reports 8 (2018).

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46087

Title: Characterization and sequencing analysis of inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA

Reviewer's code: 02728252

Reviewer's country: Egypt

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-01-29 17:44

Reviewer performed review: 2019-01-30 11:22

Review time: 17 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

It is an interesting study that characterizes inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA via sequencing analysis. There are major concerns about the manuscript 1. It should be formatted according to



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the style of the journal. 2. Great language polishing is recommended and I suggest sending the manuscript to a company editing service. 3. Figures are too much for a paper and should be condensed in panels. 4. Clear hypothesis should be added.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46087

Title: Characterization and sequencing analysis of inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA

Reviewer's code: 00504335

Reviewer's country: Ukraine

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-01-29 08:23

Reviewer performed review: 2019-01-30 11:50

Review time: 1 Day and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input checked="" type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors intended to study effects of three different proinflammatory cytokines (VCAM-1, TNF- α and IL-6) on exosome production and miRNA synthesis in human umbilical MSCs. However, VCAM-1 is not proinflammatory cytokine. It is a cell



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membrane molecule CD106 (Cluster of Differentiation 106). The purified VCAM-1 is sold by R and D Systems, but not as a cytokine. VCAM-1 plays a role as adhesive molecule in some interactions among cells or in immunoregulation, but it is not secreted cytokine. It is not possible to compare VCAM-1 with cytokines. Results are described on one and half page, but demonstrated in 13 figures and 4 tables. No figure legends are provided. The authors should ask some experienced scientist to help them with preparation of the manuscript. At the present form, the paper is not suitable for the international journal.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46087

Title: Characterization and sequencing analysis of inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA

Reviewer's code: 03370303

Reviewer's country: Japan

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-01-29 15:53

Reviewer performed review: 2019-01-31 07:19

Review time: 1 Day and 15 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this study, authors describe the differential profiles of MSC exosomes when MSCs were treated by VCAM-1, TNF- α and IL-6 to understand how the characters of MSC exosomes would change under inflammatory situations such as cancer progression.

Although the results shown in this manuscript are rather descriptive than determining/identifying/proving specific findings, it is worth reporting since it contains a large mass of valuable information with detailed analyses. However, there are several concerns in the manuscript. Before publication in World Journal of Stem Cells, they should be properly addressed. Major concerns: 1) Raw data for the integrated miRNA expression should be registered in public databases and their accession numbers should be written in the main text so that readers can share them. 2) In the second section of "Results" in page 7, the concentration of MSCs-exo for the IL-6 group was missing. Please describe the finding. Minor concerns: 1) There are several unusual (or even peculiar) usages of words, such as "precipitate" in page 2 and page 3, although it is properly used in page 5. The word "precipitate" in page 2 and page 3 should be replaced by a common word, for example, "up-regulate", "augment", "enhance", "boost" and so on. 2) There is inconsistency in the usage of the abbreviation including "MSC-exo", "TNF- " and IL6. After showing the abbreviated form in its first use, the abbreviated form should be used throughout the manuscript. 3) In page 3, the word "diseases!" should be corrected as "diseases". 4) In page 7, the sentence "Correlation analyses showed that miRNA in the IL-6 group (0.583) and TNF α group (0.697) were different than the control group." is peculiar. It should be replaced by, for example, "Correlation analyses showed that miRNA expression profile in IL-6 group (0.583) and that in TNF α group (0.697) were more different from that of the control group than that in VCAM1 group (0.985)." 5) In page 7, the sentence "Hierarchical Clustering indicated that the IL-6 group compared with the control group downregulated most kinds of expressed genes (Figure 7)." is peculiar. It should be replaced by, for example, "Hierarchical Clustering indicated that the expression levels of the majority of miRNAs in IL-6 group were downregulated compared with the control group (Figure 7)." 6) In page 8, line 4, the word "between" should be corrected as "among". The word "between"



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can only be used when comparing the two things.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46087

Title: Characterization and sequencing analysis of inflammatory factor-induced changes to mesenchymal stem cell exosomes and exosomal microRNA

Reviewer's code: 02566952

Reviewer's country: Romania

Science editor: Fang-Fang Ji

Reviewer accepted review: 2019-01-31 15:27

Reviewer performed review: 2019-01-31 16:19

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

An interesting in vitro study investigating on MSC released exosomes under inflammatory conditions, with special focus on their miRNA content. Introduction Actually MSC exosomes are NOT used clinically in any application as of yet (January



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2019) Reference cited in regard to cardiovascular diseases is a review referring to animal models of disease which stresses in itself THE NEED for clinical studies. Material and methods It is good to mention the method of “purifying” cord blood MSCs used here is one of negative magnetic separation (reader should not be obliged to know what Isolex is but the principle of the method needs to be disclosed by the authors) What was the length of MSC exposure to adhesion molecule and inflammatory cytokines? Minor typo in the bioinfo description “ functional heatmap” is maybe the correct form Results and discussion Accurate introduction of results and their discussion. I miss, however, an (at least) in vitro validation of bioinfo results (say an in vitro angiogenesis test, perhaps endothelial cells exposed to “normal” MSC-exo compared to those obtained under “inflammatory” like stimulation) The length of “inflammatory” stimulation is important as well (different exposure times should be used maybe in a further study) as this might explain the paradoxical findings reported about pro or anti angiogenetic role of MSC exo The role of intracellular signaling PI3K/ AKT is pleiomorphic and not only related to angiogenesis, its major role in cell cycle and cell quiescence could be discussed (and eventually in vitro tested as well)

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