



PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 45576

Title: Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: A concise review

Reviewer's code: 00609434

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2019-01-08

Date reviewed: 2019-01-10

Review time: 4 Hours, 2 Days

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 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 type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript from Wang et al. is a very useful review describing the application of MSC cell therapies to the treatment of osteoarthritic diseases. This review is really interesting and updated in its collection and description of current knowledge and



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clinical protocols exploring the therapeutic use of MSCs from various sources on cartilage degenerative pathologies in animal models and humans. I find it absolutely worthy of publication although in some chapters there are English syntax errors and the punctuation has to be revised before publication. In the following, the points to be revised: Page 4 lines 6-9: "Accordingly, it has been studied that connective tissue growth factory is loaded into scaffolds to assist cartilage repair and increase the degree of integration of new cartilage units with surrounding tissues [20, 21] ". What is "connective tissue growth factory"? The mentioned literature (20, 21) does not fit with the description given by the Authors, which by the way, is not clear. Page 4 lines 27-29 "Exosomes as communication carriers between cells, which primarily delivering various mRNA, microRNA, DNA proteins, lipids and other bioactive substances [24]. ". Please correct the syntax of the sentence, it lacks the main verb. Page 5 lines 1-3: "The increase in enzyme activity is proportional to the loss of normal equilibrium, i.e., exosome activates enzymes promotes tissue repair and regeneration by restoring homeostasis during injury and disease. ". Please correct "exosome activates enzymes promotes..." because it's not clear the meaning and it's grammatically wrong. Page 6 page 2-4: "MSCs can be activated by inflammatory factors, thereby making secrete PGE2, IDO, NO and other factors directly or indirectly suppress immune cells [40]. ". Please write in correct English . Page 6 lines 14-15:: "The supernatant cultured with MSCs stimulated by INF- γ and IL-1 β can increase the expression of arginine, IDO and nitric oxide synthase (iNOS) in macrophages, " . Did the authors mean "The supernatant from MSCs stimulated by INF..."? Please write in correct English. Page 6 lines 24-26: "It has been reported that cytokines secreted MSCs can target with synovial membrane and chondrocytes, so as to regulate anabolic and catabolic factors, or to induce the molecules expression of anti-inflammatory and chondrogenic [49]." Please write in correct English. Page 6 lines 30-32:" Barry and Murphy consider that [50] the function of mesenchymal stem cells



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actually originates from its paracrine mechanism, the repairing of damaged cartilage was used cells which primarily comes from the joint itself, and only a small number of foreign cells are involved during repairing, though the joint surface was repaired after the injection of mesenchymal stem cells. ". Please write in correct English. Page 7 lines 6-7:" Mixed injection means that MSCs combined with growth factor, cytokines and scaffolds for implantation, and the efficacy is improved by implantation of MSCs mixed with them. ". Please write it correctly. Page 7 lines 15-18:" If the PRP combined with MSCs (adipose mesenchymal stem cells: AD-MSCs/ vascular stroma of adipose tissue: SVF) for treating knee osteoarthritis, which can create a better microenvironment for MSCs growth (promote the blood supply, reduce the local inflammatory response), promote the synthesis of cartilage matrix and improve the therapeutic effect of stem cells in knee arthritis [52-54]. ". Please correct all the sentence because it is not possible to understand its meaning. Page 7, Table 2 title: "Summary of MSCs/PRP clinical trials in OA animal models from 2012 to 2018." Please revise the title because they are clinical studies and not animal models.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 45576

Title: Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: A concise review

Reviewer's code: 02446277

Reviewer's country: Romania

Science editor: Fang-Fang Ji

Date sent for review: 2019-01-08

Date reviewed: 2019-01-10

Review time: 4 Hours, 2 Days

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 checked="" 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

The submitted manuscript summarized the potential applications of mesenchymal stem cells in the preclinical models and clinical applications of osteoarthritis. The authors described the characteristics of MSCs, including their immunomodulatory function, and



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then continue with examples of therapeutic use of MSC used directly via intra-articular injection, seeded on scaffolds or as source of exosomes. The information included in the manuscript is correct, well presented and very useful, especially the one on MSC clinical trials for osteoarthritis diseases. A major problem is the English. Although the manuscript has a Non-Native Speakers of English Editing Certificate, the English is deficient and many phrases are unclear. Another problem is related to the abbreviation, most of them not being defined at the first time use in the text. Also, there are several orthographical errors like: phrases that ends with comma (page 6), other that starts with lower case (page 4) and other that use capital letter after colon (page 3). In conclusion, proofreading must be seriously consider. Major comments: 1. The phrase: "MSCs can serve as cartilage progenitor cells or regenerative cells to stimulate endogenous cells to be co-cultured with three-dimensional scaffolds and implanted into the target area through joint surgery to repair the damaged cartilage [18]" is unclear. Must be rewritten. 2. Explain what "the connective tissue growth factory" represents (page 4) 3. Explain how scaffold materials can cause graft rejection. I think that scaffold materials can be subject of graft rejection (page 4) 4. The use of immunomodulatory biomaterials is another interesting idea that can be mentioned (eg PMID: 25155610, PMID: 28116128) 5. "Exosomes as communication carriers" (page 4); most probably it is "Exosomes are communication carriers" 6. Please verify the following sentence: "Accordingly, microRNA may be vital to mediate MSCs exosomes in the treatment of OA" (page 4). It is unclear. 7. "Exosome activates enzymes promotes tissue repair" (page 5); the time of the verb promote is inappropriate 8. Define the abbreviation the first time you use it in the text (eg. Page 4: PLGA, PEG, PLA, PGA; Page 5: AD-MSC, HA, PRP; Table 5: ICRS, VAS, IKDC, WOMAC, VAS, SF-36, SASK, OOS, OARSI; Table 4: VAS, ICOAP, LEQUESNE) 9. Incorrect / unclear sentence "MSCs can be activated by inflammatory factors, thereby making secrete PGE2,IDO, NO and other factors directly or indirectly



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suppress immune cells [40] (page 6). 10. There are several orthographical errors like: phrases that ends with comma (page 6), other that starts with lower case (page 4) and other that use capital letter after colon (page 3). 11. Unclear phrases: “Mixed injection means that MSCs combined with growth factor, cytokines and scaffolds for implantation, and the efficacy is improved by implantation of MSCs mixed with them.” “If the PRP combined with MSCs (...) for treating knee osteoarthritis, which can create a better microenvironment for MSCs growth (...), promote the synthesis of cartilage matrix and improve the therapeutic effect of stem cells in knee arthritis (page 7) 12. Table 2: a clinical trial cannot be on animal models. It can be referred as pre-clinical trial trials or non-clinical models.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 45576

Title: Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: A concise review

Reviewer's code: 00573611

Reviewer's country: Taiwan

Science editor: Fang-Fang Ji

Date sent for review: 2019-01-08

Date reviewed: 2019-01-13

Review time: 21 Hours, 4 Days

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 checked="" 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

In this review article, the authors reviewed the potential applications of mesenchymal stem cells in the preclinical models and clinical applications of osteoarthritis. The authors reviewed the contents of preclinical and clinical trials in the recent 3 years and



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suggested that intra-articular injection of MSCs can lead to the reduction of index-pain, improve the function and significantly increase the volume of cartilage. Comments This is an interesting review article. The review has some minor concerns as follows: 1. An abbreviation first time used in the text present both the spelled-out version and the short form: AD-MSCs, UC-MSCs, PRP, etc. 2. In Table 1, the authors summarized mesenchymal stem cell preclinical trials in OA animal models from 2015 to 2018, but there is no study on 2015. Moreover, are there any rodents-mouse/rat data for this issue? 3. In Table 2 title: "Summary of MSCs/PRP clinical trials in OA animal models from 2012 to 2018", deleted the description of "in OA animal models", it is the clinical trial. Moreover, there is no study on 2018 in this Table. 4. In the clinical trials, are there any immunosuppressant drugs used?

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 45576

Title: Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: A concise review

Reviewer's code: 02446242

Reviewer's country: Italy

Science editor: Fang-Fang Ji

Date sent for review: 2019-01-08

Date reviewed: 2019-01-14

Review time: 1 Hour, 6 Days

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 polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

The review is well written and includes most of the literature on this topic, analyzing the issues and the advantages of MSC treatment of OA.



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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 45576

Title: Application of mesenchymal stem cells therapy in the treatment of osteoarthritis of the knee: A concise review

Reviewer's code: 02446054

Reviewer's country: United States

Science editor: Fang-Fang Ji

Date sent for review: 2019-01-08

Date reviewed: 2019-01-14

Review time: 12 Hours, 6 Days

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 checked="" 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
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SPECIFIC COMMENTS TO AUTHORS

see document attached

INITIAL REVIEW OF THE MANUSCRIPT



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