



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46763

**Title:** Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation

**Reviewer's code:** 02566952

**Reviewer's country:** Romania

**Science editor:** Ying Dou

**Reviewer accepted review:** 2019-07-15 08:12

**Reviewer performed review:** 2019-07-15 08:56

**Review time:** 1 Hour

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**

A well written good conceived manuscript presenting tendon structure metabolism and ageing processes together with potential methods for quenching degradative phenomena due to aging. Comments .Introduction Well written Stem cells can be pluripotent however they are as well varieties that are multipotent, restricted to the



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embryonic layer of origin (such as MSCs). The phrase starting with “recently discovered iPSCs is unclear and way too long, Please reformulate in a way the message can be conveyed. The myth of MSC immune privilege is somehow contested these days , would be important to note this See Berglund et al Stem Cell Resources and Therapies , 2017. Proliferative capabilities could help TSCs while transplantation, however I am not sure this is the case with multilineage differentiation. One needs TSCs to differentiate to tenocyte when healing tendon not to develop adipo, oste or chondrocytes for example. PRP role in stimulating tendon healing should as well regarded with caution and by discriminating dosage, modalities of use and growth factor profile. High concentration of PRP together with increased VEGF content have been reported to be detrimental for tendon healing (See Gusti et al Biomed Res Int 2014) Maybe inserting a small table summarizing the effect of known pharmacological agents on TPSCs would improve the clarity of this chapter A morphological description of aging tendons could help the reader visualize what the authors are describing. Is there a correlating between morphological aspects of tendon aging and tendon degeneration (tendinosis) Are tendon stem cells implicated in occurrence of degenerative zones ? What is the current knowledge in this respect? When describing the role of cellular cytoskeleton and surface adhesion markers one should at least mention the interaction with ECM and role of stem cell niche within ageing as the physical biochemical changes that occur in ECM proteins are likely to highly influence both stem cell maintenance and turnover Reader is informed about limited studies regarding the role of several proposed antiageing compounds on tendon stem cells. It is not clear what limited means, are there any (if so please cite) ore there is to date a complete lack of such studies?

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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46763

**Title:** Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation

**Reviewer's code:** 02728252

**Reviewer's country:** Egypt

**Science editor:** Ying Dou

**Reviewer accepted review:** 2019-07-15 07:35

**Reviewer performed review:** 2019-07-17 08:05

**Review time:** 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 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 checked="" 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 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**

It is a comprehensive narrative review about tendon stem/progenitor cell ageing: modulation and rejuvenation. It is an interesting review, well-constructed but need English language editing.



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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46763

**Title:** Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation

**Reviewer’s code:** 02446120

**Reviewer’s country:** Argentina

**Science editor:** Ying Dou

**Reviewer accepted review:** 2019-07-15 12:26

**Reviewer performed review:** 2019-07-17 18:35

**Review time:** 2 Days and 6 Hours

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:
<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 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**

Review; Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation Comments to the authors The manuscript by Guang-chun Dai et al, describes the role of Tendon Stem/Progenitor Cells (TSPCs) during aging, or processes leading to deterioration of tendons’s structure and function. More precisely, the authors focused on the incidence of



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growth factor decreases and hormone deficits on tendons' diseases. They also gathered evidences that addition of suitable extracellular matrix (ECM), growth factor or hormones improved TSPCs functions. The review is relevant since the isolation and identification of TSPCs in tendon fascicles of many animals is rather recent. Therefore, these cells could be used for regeneration of tendon tissues. Particularly interesting in this review are the facts that moderate mechanical stretching up-regulates stem markers and the importance of controlling environmental cues and signaling mechanisms. In general, the manuscript opens an additional and interesting way of treating tendons, by focusing on reactivation of TSPCs for treatment of tendon-related diseases. Major concerns - "It is estimated that there are 0.96 billion elderly people over the age of 60 worldwide in 2017, and this population is growing at the fastest rate. Moreover, nearly 150 thousand people will die each day all over the world with two thirds of these deaths caused by age-related reasons, indicating that ageing is a vital risk factor for numerous age and degeneration-related diseases, Authors: it seems obvious the fact that ageing is a vital risk. Please delete the phrase and focus the text on how ageing could affect tendon damages, instead. - Stem cells are pluripotent cells that can differentiate into various tissue types under different conditions and serve as an internal repair system Authors: the phrase is imprecise, there are different stem cell types and not all of them can differentiate into various tissue types (i.e.: unipotent stem cells) . Please, rephrase as follows: Pluripotent Stem cells can differentiate into various tissue types under different conditions and serve as an internal repair system Minor issues - "In adults, TSPCs, a type of MSC, were first confirmed to be present in tendon tissues by Bi et al. in the year of 2007", Authors please expand "MSC" - In the MSC ageing process, the p16/RB pathway and p53/p21 pathway have vital roles in affecting the cellular senescence though regulation of telomere length and function Authors: though or through?



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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46763

**Title:** Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation

**Reviewer's code:** 03471268

**Reviewer's country:** Japan

**Science editor:** Ying Dou

**Reviewer accepted review:** 2019-07-15 05:02

**Reviewer performed review:** 2019-07-18 07:28

**Review time:** 3 Days and 2 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

In this review, the authors summarize the TSPCs characteristics, their epigenetic variations associated with ageing and some rejuvenation methods. There are some comments. 1. The author used different terms to describe the tendon-related stem cells, such as TSPCs, TDSCs and TSCs. The point is, are they the same thing? If so, it is better



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to use single term to avoid misunderstanding. If not, the authors should give clear definitions of each of them to help the audience to distinguish them. In addition, “TPSCs” was also found. Is it an error? 2. In the part of “Rejuvenation of aged tendon stem/progenitor cells”, it is mentioned that “Numerous factors, including exercise, estrogen fluctuation, ECM conditions, and drug uses, affect the features that are altered in TSPCs upon the influence of age, and these alterations are primarily harmful to TSPC function and maintenance of tendon homeostasis.” My questions are: 1) Does it mean the exercise is harmful to TSPC function? However, the following citation indicated that “Moderate exercise ameliorates the deteriorative condition of the TSPC”. I think the author must clarify these descriptions. 2) It seems inappropriate to discuss these factors together. “Exercise” is from a macroscopic view while “estrogen fluctuation, ECM conditions, and drug uses” may be from a microscopic view. 3. Due to the latest development of regeneration medicine, the authors should review and add comments on the literature about pluripotent stem cell-derived tenocytes or their progenitor cells. These new experiments should be very informative for the rejuvenation of tendon in the future.

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**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Stem Cells

**Manuscript NO:** 46763

**Title:** Tendon Stem/Progenitor Cell ageing: modulation and rejuvenation

**Reviewer's code:** 01851506

**Reviewer's country:** Japan

**Science editor:** Ying Dou

**Reviewer accepted review:** 2019-07-15 23:53

**Reviewer performed review:** 2019-07-19 02:11

**Review time:** 3 Days and 2 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 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 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**

In this manuscript Dai et al have discussed the potential, the nature, and inherent problems of Tendon stem/progenitor cells (TSPCs) for tissue repairing. The content is in general interesting. However, the text is not reader-friendly, especially for those who are not in the field. For example, there has been no introduction for A-TSPCs and



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Y-TSPCs in the text (page 8). The same is true for TSPCs 7d, TSPCs 1d, and TSPCs 56 d (page 8-9). Such abbreviations should be clearly defined at the first time when they are used. There are so many in the text. Besides the above critiques, the reviewer does not agree with the notion that IL-6 is anti-inflammatory cytokines. Since IL-6 is generally considered to be an inflammatory cytokine, while IL-10 to be an anti-inflammatory one (page 6). In addition, another figure illustrating the problems in the aged TSPCs relative to the young TSPCs would help readers follow the context. Finally, the reviewer strongly suggests the paper to be edited by (a) professional English editor(s).

#### **INITIAL REVIEW OF THE MANUSCRIPT**

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