



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 00609371

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-04-26

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 concerns are: 1) how does the cell renewal ability correlate with ALDH activity? 2) does this has anything to do with constitutive vs inducible form of ALDH? 3) what's the specific clinical implication of this study? 4) Adherent ADSCs from passage 4 were used, why? is it possible to use the freshly isolated cells? 5) the final conclusion is incomplete



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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 03478635

**Reviewer's country:** Japan

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-04-27

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**

1. In Cell differentiation and immunofluorescence staining subsection of method section, culture days for the adipogenic and osteogenic differentiation of ADSCs may be added.
2. In Cell differentiation to adipocytes and osteocytes subsection in result section, Fig.2B seems to indicate adipogenic differentiation, although it is described as osteocytes in the text. Please carefully check them.
3. In conclusion section, the description about ribosome should be completed.



## PEER-REVIEW REPORT

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 02446280

**Reviewer's country:** Russia

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-02

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [ Y] 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		[Y] No	<input type="checkbox"/> [ ] Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

### COMMENTS TO AUTHORS

The paper is well written and provides comprehensive data on the ALDH activity usefulness for murine cells.



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 00504800

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-04

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 authors use ALDH to sort an enriched stem cell population from murine ADSC. While by itself this is not terribly exciting, it does provide additional potential evidence between human and murine MSC, and perhaps between ADSC and other MSC sources. Of note, the finding of increased ribosome-related gene expression is potentially the most interesting finding of the manuscript, given recent interest in this topic, although this requires more discussion. Items to address: The Abstract is brief and choppy. Gene set analysis is not mentioned in the Abstract methods, nor is the finding that ribosome-related genes have increased expression mentioned in the Abstract conclusion - I would think these are important to note in the Abstract. The Methods can be shortened, particularly when referring to a product and stating that "the manufacturer's instructions were followed". There are more papers now available on the topic of



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ribosome biogenesis and the regulation of stem cells. The authors spend only one short paragraph on this in the Discussion. Since this is potentially the most interesting finding of the manuscript (it already being known that ALDH can be used to sort/enrich various stem cell subsets), I would recommend that the authors enhance their discussion of stem cell regulation by ribosomes. In the final conclusion, the last sentence was cut off - please correct this.



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 01554116

**Reviewer's country:** Spain

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-05

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [ Y] Accept
<input type="checkbox"/> [ Y] Grade B: Very good	<input type="checkbox"/> [ Y] 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		[Y] No	<input type="checkbox"/> [ ] Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

**COMMENTS TO AUTHORS**

This is a fine manuscript describing the immunophenotypic characterization of a subpopulation of adipose-derived mesenchymal stem cells that present genomic and functional characteristics. The work is well designed and performed, and the conclusions are supported by the results. The final phrase in the Conclusion appears to be cut in the middle of the sentence.



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## PEER-REVIEW REPORT

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 02445899

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-05

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
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<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

Many thanks for the opportunity to review the article of Itoh et al. This is a very interesting and well executed piece of work, with suitable controls. An additional marker for a sub-population of ADSCs with preponderance to osteogenic and adipogenic differentiation is described and discussed in some detail, which adds to the current literature and knowledge about the heterogeneity of SC populations in general. The abstract requires some attention to the English, but otherwise the article is clearly written. I recommend that the article be published.



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 01851506

**Reviewer's country:** Japan

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-09

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"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

**COMMENTS TO AUTHORS**

Comments to the authors General comments Itoh and colleagues have addressed the potential difference in differentiation between aldehyde dehydrogenase (ALDH)high subset and ALDHlow subset in the murine adipose-derived stem cells (ADSCs). They found that ALDHhigh subset has a strong propensity to differentiate into adipocytes and osteocytes as compared to ALDHlow subset accompanying upregulation of the genes relevant to the protein synthesis. Although the data are potentially interesting, there are several concerns. (1) While they show the ALDHhigh subset in Figure 1A, ALDHlow subset is not indicated. This makes it impossible to review the results that they present here. (2) Though the authors use the mean, t-test, and one-way ANOVA for statistics, how they are sure that the data with which they deal are "parametric"? (3) While the authors report the difference in differentiation potential between ALDHhigh



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subset and ALDHlow subset through visualization with the differentiation markers such as FABP4 and osteopontin (Figure 3), they do not observe any difference in transcripts pertinent to the adipocytes and/or to the osteocytes except for those implicated in the protein synthesis in the Gene Set Enrichment Analysis (Figure 4). This should be explained. (4) Data are poor to support the conclusions of the authors. Minor points (1) English needs to be polished. (2) Materials and Methods section should be more concise. (3) What stands for " cell proliferation rate" in Figure 1B?



**PEER-REVIEW REPORT**

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

**Manuscript NO:** 34298

**Title:** Aldehyde dehydrogenase activity helps identify a subpopulation of murine adipose-derived stem cells with enhanced adipogenic and osteogenic differentiation potential

**Reviewer's code:** 01047169

**Reviewer's country:** South Korea

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-04-26

**Date reviewed:** 2017-05-10

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
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<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**

This manuscript newly identified ALDH activity as a marker for adipose-derived stem cells subpopulation with higher potential of differentiation into adipocytes and osteocytes. Although ALDH activity was implicated in other stem cells and cancer cells, it was not reported in adipose-derived stem cells. Therefore, this information can provide better understanding and application. However, there are some points to be revised. 1. Please check whether the indication of figures are right and enough at the present form. On page 14, in the middle. "ADSCs that differentiated into adipocytes appeared as accumulated lipid droplets in the cytosol in each ALDH<sup>Hi</sup> and ALDH<sup>Lo</sup> subpopulation (Fig. 2A-B?). Furthermore, antiosteopontin(?? It's not clear) immunofluorescence staining revealed that ADSCs that differentiated into osteocytes appeared as accumulated granules in the cytosol in each ALDH<sup>Hi</sup> and ALDH<sup>Lo</sup>



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subpopulation (Fig. 2C-D?)” 2. There seem some missing sentences in the last part of page 18. “Ribosome biosynthesis is” What? 3. Figure 2 and 3 can be combined. In that way, it is easier to understand the data. 4. In Figure 2B, the cell numbers are too small, therefore it is difficult to compare the differentiation efficiency. In addition, investigation on at least two markers per each cell-type differentiation is recommended to make sure.