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JOURNAL EDITOR-IN-CHIEF'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 81791

Title: Bone marrow mesenchymal stem cell-derived exosomal microRNAs target PI3K/Akt signaling pathway to potentially promote tendon-bone healing

Journal Editor-in-Chief (**Associate Editor):** Shengwen Calvin Li

Country/Territory: United States

Editorial Director: Jia-Ping Yan

Date accepted review: 2023-03-05 17:27

Date reviewed: 2023-03-05 19:37

Review time: 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Rejection
[ ] Grade D: Fair		[Y] Minor revision
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Major revision

JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

Comment: The manuscript claimed, "MSC-derived exosomes promote fibroblast activation, possibly through the PTEN and PI3K/Akt signaling pathways, which may serve as potential targets to further promote tendon-bone healing," solely based on the NIH3T3 cell model. The caveat was "Tendon is a relatively simple tissue, with one predominant cell type—fibroblasts, which in tendon are called tenocytes and embedded in an insoluble matrix of elongated collagen fibrils that are surrounded by a soluble compartment of glycoproteins including proteoglycans." Thus, tendon-bone-associated fibroblasts differ from the NIH3T3, with a modal chromosome number of 68 (Specific comment #15 below). Second, they did not specifically isolate MSCs-exomes on tenocytes, thus providing circumstantial data to claim the point. The authors need to address the following specific comments to improve clarity by thoroughly defining the limitations of the current version of the manuscript. Specific comments: 1) The title overstated their data (refer to the above comment).

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2) Abstract: "the underlying mechanism is not comprehensive understood." Use [comprehensively]. 3) Abstract: "Herein, this study aimed to identify the exosomal miRNAs universally carried by MSC-derived exosomes, and to verify their effects as well as mechanisms on fibroblasts." How did they define "universally?" As in the current version, neither its theory nor the experimental data justified such a term. 4) "AIM: To identify the exosomal miRNAs universally carried by MSC-derived exosomes" – How did they define MSC-derived? MSCs are diversified in different contexts – what is their specific context? Refer to "doi: 10.1089/hum.2010.115 Bone marrow mesenchymal stem cells: historical overview and concepts. Please note that "In an attempt to standardize the definition of an MSC, the International Society for Cellular Therapy (ISCT) proposed the concept of essential minimal criteria for MSCs in culture. The four minimal defining criteria for MSCs are: i) adherence to plastic under standard tissue culture conditions ii) expression of CD105, CD73, CD90 iii) lack of expression of CD45, CD34, CD14/CD11b, CD79/CD19 and HLA-DR surface markers and iv) differentiation into adipocytes, osteoblasts and chondroblasts in vitro [Dominici M, et al. Cytotherapy 8: 315-317, 2006]. Nevertheless, there is no consensus regarding the MSC phenotype, because of the broad variety of potential tissue sources and the differences in cell isolation and cell culture procedures used. In addition, differences in media formulations (FBS, platelet lysates, growth factor combinations), plating density and oxygen tension may affect the gene profile, epigenomic state and phenotype of the mesenchymal population" –[Roobrouck VD et al. Stem Cells 4: 583-589, 2011]. Along with these lines, what QC guidelines did they use in their MSCs? 5) Page 5: "Recent evidence indicates that conditioned medium, primarily contains [containing] exosomes of MSCs, can stimulate the activation of fibroblasts, thereby promoting tendon-bone healing[9-12]." 6) Page 6: "Three MSC-derived exosomal miRNA expression microarray datasets (GSE71241, GSE153752, and GSE85341) were retrieved from the GEO repository (https://www.ncbi.nlm.nih.gov/geo)." The day of access should be provided. 7) Figure 2. All the species of miRNAs should be supplemented in Excel files. 8) Figures 3, 4, 5. All the species of genes should be supplemented in Excel files. 9) Figure 6D, E, F, G. How did they titrate "The relative luciferase activity of WT-PTEN and MUT-PTEN in NIH3T3 cells co-transfected with miR-23b-3p mimics and pmirGLO-PTEN-3'UTR vector" to avoid squelching effects? 10) Fig7A, B: scale bars are needed. 11) Fig 7C. the scale bars seemed way off the number as marked. 12) Fig 8. scale bars are needed. 13) Fig 7. "fibrosis of NIH3T3 fibroblasts" – How did they determine the fibrosis? 14) Fig 7. "COL I and α-smooth muscle actin positive expression." How did they specify muscle actin? 15) Fig 9. "Figure 9 Inhibition of phosphatase and tensin homolog promoted fibroblastic, tenogenic, and chondrogenic potential of NIH3T3 cells" How did they alternatively verify these claims? Please note that "What does NIH3T3 stand for? They were obtained from desegregated NIH Swiss mouse embryo fibroblasts by George Todaro and Howard Green. 3T3 stands for "3-day transfer, inoculum 3×105 cells" and is derived from the original cell transfer and inoculation protocol." The spontaneously immortalized cells with stable growth rate were established after 20 to 30 generations in culture, and then named '3T3' cells. Since then, several cell lines have been established with this

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procotol:[3] 3T3-Swiss albino, the original 1962 cell line 3T3-J2, a subclone of 3T3-Swiss albino, commonly used as feeders for keratinocyte cultures[4] 3T3- Y, a subclone of 3T3-Swiss albino, used as a model of adipogenesis[5] NIH-3T3, also from Swiss albino mice BALB/c-3T3 clone 1, from BALB/c mice. " "Cytogenetics 3T3 mouse cells are hypertriploid. The modal chromosome number is 68, which occurs in 30% of cells. Higher ploidies occur at a much lower rate of 2.4%." Ideally, they must follow the model by Taylor, S.E., Vaughan-Thomas, A., Clements, D.N. et al. Gene expression markers of tendon fibroblasts in normal and diseased tissue compared to monolayer and three dimensional culture systems. BMC Musculoskelet Disord 10, 27 (2009). https://doi.org/10.1186/1471-2474-10-27. These experiments could be shown in Wang X. T., Liu P. Y., Xin K.-Q., Tang J. B. (2005). Tendon Healing In Vitro: bFGF Gene Transfer to Tenocytes by Adeno-Associated Viral Vectors Promotes Expression of Collagen Genes. J. Hand Surg. 30 (6), 1255–1261. doi:10.1016/j.jhsa.2005.06.001. 16) Page 14: "Normal TBI has a transitional structure consisting of four gradated [? graduated] layers, including bone tissue, mineralized fibrocartilage layer, non-mineralized fibrocartilage layer, and tendon tissue[27],"