

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 76480

Title: Application of exosome-derived noncoding RNAs in bone regeneration: Opportunities and challenges

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05480683

Position: Peer Reviewer

Academic degree: PhD

Professional title: Academic Fellow, Academic Research, Adjunct Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2022-03-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-03-19 19:38

Reviewer performed review: 2022-03-27 10:59

Review time: 7 Days and 15 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The review manuscript (Manuscript ID: 76480) entitled “Application of exosome-derived noncoding RNAs in bone regeneration: Opportunities and challenges” by Dr. Ren provides a detailed overview on the the biogenesis of exosome-derived ncRNAs and the effects of ncRNAs on angiogenesis and osteoblast- and osteoclast-related pathways in different diseases. While several improvements can be made in the introductory section, the review manuscript is in general concise, well written, informative and well organized. The work includes important data on the role of non coding RNAs, including lncRNAs, miRNA and circRNAs in osteogenic differentiation. I therefore recommend a minor revision. I have several suggestions for improving the manuscript: Major comments 1. A brief description of the noncodingRNA / miRNA biogenesis might be helpful for the reader. Authors can check: PMID: 26666209 2. The main pathways involved in the osteogenic differentiation, i.e. Transforming Growth Factor-beta (TGF- β)/bone morphogenic protein (BMP) and the Wingless/Int-1(Wnt)/ β -catenin pathways, should be at least briefly quoted in the “Bone regeneration” paragraph. Several introductory sentences can be moved from the “Regulatory mechanisms of exosome-derived miRNAs in osteogenic differentiation” to the “Bone regeneration” paragraph 3. Since being too short, several paragraphs, such as “Regulatory mechanisms of circRNA in osteogenic differentiation”, “Roles of exo-ncRNAs in angiogenic differentiation”, “Regulatory mechanisms of lncRNAs in angiogenic differentiation” Regulatory mechanisms of miRNAs in osteoclast differentiation” Regulatory mechanisms of lncRNAs in osteoclast differentiation” “Regulatory mechanisms of circRNA in osteoclast differentiation” can be merged to the

main respective paragraphs on ncRNAs, miRNAs and circRNAs and osteoclast differentiation. Alternatively, they can be moved, as subparagraphs, under the main ones 4. As correctly stated by the authors, ncRNAs that have functional roles in regulating the expression of protein-coding genes. However other details on ncRNA function should be included. Indeed, these molecules are involved in a variety of physiological functions, while their dysregulation has also been implicated in human diseases. Previous investigations have reported that a variety human diseases, such as orthopedic (DOI 10.1093/database/baz126) and cancer diseases (DOI 10.1158/0008-5472.CAN-16-2634) as well as infertility in males (DOI 10.3389/fcell.2021.689624) were associated with deficiency, mutation, or overexpression of lncRNAs. For instance, several lncRNAs, such as H19 (which play a key role in osteogenic differentiation), as well as others, have been reported as dysregulated (in this case, by epigenetic impairments) in relation to male infertility (DOI 10.3389/fcell.2021.689624). For completeness, brief notions on lncRNAs and human diseases should be included. 5. The fact that several studies evaluated functionally the role of ncRNAs, miRNAs and circRNAs upon osteoclast differentiation with animal models should be underlined when the studies are described throughout the text

Minor observations ABSTRACT Better “microRNAs (miRNAs), long noncoding RNAs (lncRNAs)” EXOSOMES AND NONCODING RNA 1. Better microRNAs (miRNAs) when mentioned for the first time REGULATORY MECHANISMS OF LNCRNAs IN OSTEOGENIC DIFFERENTIATION 2. A detailed description of the role of lncRNAs on osteogenic differentiation is also reported here PMID: 33898434 and here doi.org/10.1177/2472751221999229. These references should be included 3.

Additional lncRNAs such as MEG3 (doi: 10.1007/s11010-017-3015-z also reviewed here PMID: 33898434), LINC00707 (doi: 10.1186/s13287-019-1161-9), PCAT1 (doi: 10.1002/jcp.28550), Rmst (doi: 10.18632/aging.102583) have recently been described as



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

implicated in osteogenic differentiation. Authors should include these lncRNAs and supporting references

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Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Indonesia

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

-The abstract and title reflected the main subject -Reference no 12 is missing on the paragraph -Some mistyping words -In general : This manuscript is too long for publishing in journal , the author is better reducing it and emphasizing in some critical points