Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: -The abstract and tittle 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

Response: We sincerely appreciate the valuable comments. The reference 12 has been added to the revised manuscript (page 5, lines 2). The final manuscript was send to a language editing company to improve the article for language and the certificate was provided in the attachment. We highlight some key points in the article (page 9, lines 12, page 11, lines 16 and page 13, lines 10).

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
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 introductive 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

Response: Thanks a lot for your meaningful suggestion. The description of the noncodingRNA/miRNA biogenesis have been added to the revised manuscript（page 6 , lines 5 to 11 ）.

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 introductive sentences can be moved from the "Regulatory mechanisms of exosome-derived miRNAs in osteogenic differentiation" to

the “Bone regeneration” paragraph

Response: Thanks for your advice. "The main pathways involved in the osteogenic differentiation" have been quoted in the paragraph "Bone regeneration" (page 7, lines 1 to 6). The introductory sentences have been moved from the “Regulatory mechanisms of exosome-derived miRNAs in osteogenic differentiation” to the “Bone regeneration” paragraph (page 7 , lines 1 to 6).

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

Response: We sincerely appreciate the valuable comments. “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” have be merged to into the main respective paragraphs on ncRNAs, miRNAs and circRNAs and osteoclast differentiation(page 9 , lines 12; page 11, lines 16 and page 13 , lines 10).

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.

Response: Thank you for your careful review. The notions on lncRNAs and human diseases have been added to the revised manuscript (page 9, lines 15 to 18).

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

Response: Thank you for your careful review. The description of animal models has been added to the revised manuscript（page 13 , lines 17 to 21 and page 13, lines 26 to 27 ）.

Minor observations ABSTRACT Better "microRNAs (miRNAs), long noncoding RNAs (lncRNAs)" EXOSOMES AND NONCODING RNA

Response: Thanks a lot for your meaningful suggestion. "microRNAs (miRNAs), long noncoding RNAs (lncRNAs)" have been added to the revised manuscript（page 3, lines 9 to 10 and page6 , lines 3 to 4 ）.

1. Better microRNAs (miRNAs) when mentioned for the first time REGULATORY MECHANISMS OF LNCRNAS IN OSTEOGENIC DIFFERENTIATION

Response: Thank you for your comments. As suggested, microRNAs (miRNAs) have been added to the revised manuscript（page 9 , lines 19）.

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

Response: Thank you for your careful review. The two references (PMID: 33898434 and here doi.org/10.1177/2472751221999229) have been added to the revised manuscript（page 9 , lines 20 to 24）.

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

Response: Thanks for your advice. Additional lncRNAs including MEG3, LINC00707, PCAT1 and Rmst have been added to the revised manuscript（page 9 , lines25 to page 10, lines 5）.

(1) Science editor:

The authors reported that there are still many unsolved problems and challenges in the clinical application of many MSc derived ncRNAs. The author's writing level is very good and logical, but it is not a very novel topic. There are some small problems that need to be corrected. There are many differences in the source of MSC. The source of MSC should be noted in the author's table. The article needs a great deal of language polishing.

Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Response： We sincerely appreciate the valuable comments. Source of MSC in author table have been added to the revised manuscript （Table 1 , column 1 ）. The final manuscript was send to a language editing company to improve the article for language and the certificate was provided in the attachment.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/.

Response： We sincerely appreciate the valuable comments. We have used reference citation analysis (RCA) in the revised manuscript. Since reference 96 is not indexed by Pubmed, we provide the full text of the article and mark it in yellow in the reference list.(96 **Ahmad P**, Stoddart M J, Della Bella E. The role of noncoding RNAs in osteogenic differentiation of human periodontal ligament stem cells. Craniomaxillofacial Trauma & Reconstruction Open 2021; **6:** 1-13 [DOI: 10.1177/2472751221999229]). We understand that no more than three citations from the same journal and amend the reference list accordingly. However, there are two significant journals (*Stem Cell Res Ther* and *J Cell Mol Med*) in the article with four citations each, and we hope these citations will be retained.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing

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Response: Thanks for your advice. We process the forms strictly according to the magazine requirements. The re-used images have been approved by the original publisher. The reference source and copyright are correctly indicated.

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