Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The manuscript "MiR-584-5p/RUNX2 Axis Mediates Hypoxia-Induced Periosteal Stem Cell Osteogenic Differentiation" by Jia-Jia Lu explore the impact of the miR-584-5p/RUNX2 axis on hypoxia-induced osteogenic differentiation of PSCs. Overall, this study was well conducted with good methodology and intelligible English. It is well written and highly interesting. Their findings may provide a mechanism for PSC osteogenic differentiation and modulating miR-584-5p and miR-584-5p/RUNX2 might be a new strategy for bone repair and regeneration. The experiment of this study is designed very well. The methods of data analysis are very clear, and the results are presented well. However, the following points must be considered before publication. In my opinion, note that the additional expanded discussions are mandatory. Thank you for giving opportunity to review this study.
Reply: Thank you for your generous suggestions and affirmation of this study. We have expanded the additional discussions in the revised manuscript.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Thank you very much for asking me to review this manuscript by Jia-Jia Lu et al. This is a basic study to explore the underlying mechanisms of hypoxic environment during bone healing in regulating the differentiation of PSCs into osteoblasts or chondrocytes. The result of the study is of interest and may provide a new mechanistic insight into the regulation of PSC osteogenic differentiation induced by hypoxia. Overall, the manuscript is well designed and written. It might provide a mechanism for PSC osteogenic differentiation. Furthermore, minor comment that I would to proposed: 1. Title: Proper and cover all the core result from the study. 2. Abstract: should be revised. An informative, structured abstract is needed. A structured abstract should include at least such as background, aim, methods, results, and conclusions. It should also address all of the important component from the study. 3. Key words: could cover this study. 4. Introduction: Describe the overall basic knowledge for this study. Moreover, the aim of the study is clear. 5. Method: The present study is methodologically well conducted. 6. Results: The result of this study is of interest. 7. Discussion: The manuscript clearly interprets the finding adequately and appropriately. In addition, the manuscript highlights the key points clearly. The previous significant paper involved were included in the discussion. 8. Figures: I

congratulate the authors for the captions to the figures very explicative and complete. 9. References: The manuscript reviewed previous related literature. Also, the writing language of the article is very successful. This article is a guide for future work.

Reply: Thank you for your generous suggestions and affirmation of this study, we have carefully modified the manuscript according to the advise.

We have modified the abstract to be more informative and structured as "Background: The hypoxic environment during bone healing is important in regulating the differentiation of periosteal stem cells (PSCs) into osteoblasts (OBs) or chondrocytes; however, the underlying mechanisms remain unclear. Aim: This study aimed to determine the effect of hypoxia on PSCs, and the expression of miR-584-5p and RUNX2 in PSCs was modulated to explore the impact of the miR-584-5p/RUNX2 axis on hypoxia-induced osteogenic differentiation of PSCs. Methods: In this study, we isolated primary mouse PSCs and stimulated them with hypoxia, and the characteristics and functional genes related to PSC osteogenic differentiation were measured. Constructs expressing microRNA-584-5p (miR-584-5p) and RUNX family transcription factor 2 (RUNX2) were established for determining PSC osteogenic differentiation. Results: Hypoxic stimulation induced PSC osteogenic differentiation, and significantly increased the calcified nodules, intracellular calcium ion level, and alkaline phosphatase (ALP) activity in PSCs. The osteogenic differentiation-related factors such as RUNX2, bone morphogenetic protein 2 (BMP2), hypoxia-inducible factor 1-alpha (HIF-1α), and ALP were upregulated; in contrast, miR-584-5p was downregulated in these cells. Furthermore, upregulation of miR-584-5p significantly inhibited RUNX2 expression and hypoxia-induced PSC osteogenic differentiation. RUNX2 was the target gene of miR-584-5p, antagonizing miR-584-5p inhibition on hypoxia-induced PSC osteogenic differentiation. Conclusion: Our study showed that the interaction of miR-584-5p and RUNX2 could mediate PSC osteogenic differentiation induced by hypoxia."