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JOURNAL EDITORIAL BOARD'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 89703

Title: Unveiling the role of hypoxia-inducible factor 2alpha in osteoporosis: Implications for bone health

Journal Editor-in-Chief/Associate Editor/Editorial Board Member: Carlo Ventura

Country/Territory: Italy

Editorial Director: Jia-Ping Yan

Date accepted review: 2024-02-18 11:27

Date reviewed: 2024-02-20 11:56

Review time: 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[Y] Accept
[ ] Grade B: Very good	[ ] 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		[ ] Minor revision
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Major revision

JOURNAL EDITORIAL BOARD COMMENTS TO AUTHORS

In this research article the Authors aimed at investigating the effect of HIF-2α on the osteogenic and adipogenic differentiation of BMSCs and the hematopoietic function of hematopoietic stem cells (HSCs) in the BM niche in the progression of osteoporosis. The Authors used mice with BMSC-specific HIF-2α knockout (Prx1-Cre;Hif-2αfl/fl mice) for in vivo experiments, and by the aid of microcomputed tomography they found that the femoral bone density was lower in Prx1-Cre;Hif-2αfl/fl mice than in Hif-2αfl/fl mice under three intervention conditions designed to challenge bone homeostasis, including bilateral ovariectomy, semilethal irradiation, and dexamethasone treatment. In in vitro experiments, exposure of BMSCs from Hif-2αfl/fl mice to the HIF-2α agonist Roxadustat induced a decrease in adipogenic commitment, while leading to an increase in osteogenesis. The opposite effects were obtained following BMSCs treatment with the HIF-2α inhibitor PT2399. By the aid of the mTOR inhibitor rapamycin the Authors found that HIF-2α

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regulated BMSC osteogenic and adipogenic differentiation by inhibiting the mTOR pathway. On the whole, this is a well conducted investigation, and I found that the Authors have incorporated the criticisms and suggestions raised by the Reviewers who had the chance to assess a previous version of the manuscript. While this study doesn't disclose a novel field, as the role of HIF-2α in the modulation of adipogenesis and osteogenesis has been already investigated, even from a mechanistic standpoint, the article itself describes and characterizes in detail the interplay between HIF-2α and mTOR patterning. This issue has been only marginally discussed previously (for a review article see: Hypoxia-Inducible Factors Signaling in Osteogenesis and Skeletal Repair. Qin Q, et al. Int J Mol Sci. 2022. PMID: 36232501), and the current study adds some remarkable additional cue.