



**Baishideng
Publishing
Group**

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

PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 98911

Title: Fat mass and obesity-associated protein in mesenchymal stem cells inhibits osteoclastogenesis via lnc NORAD/ miR-4284 axis in ankylosing spondylitis

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08112959

Position: Peer Reviewer

Academic degree and professional title: N/A

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2024-07-09

Reviewer chosen by: Yu-Fei Wei

Reviewer accepted review: 2024-08-15 04:15

Reviewer performed review: 2024-08-22 12:47

Review time: 7 Days and 8 Hours

Scientific quality	Grade A (Excellent)
Novelty of this manuscript	Grade A (Excellent)
Creativity or innovation of this manuscript	Grade A (Excellent)
Scientific significance of the conclusion in this manuscript	Grade A (Excellent)
Language quality	Grade A (Excellent)
Does this manuscript describe a study of	No



the existing knowledge system?	
Does this manuscript report a revolutionary innovation?	Yes
Does this manuscript report an unconventional innovation?	Yes
Conclusion	Accept (High priority)
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

SPECIFIC COMMENTS TO AUTHORS

This article provides a potential target for the treatment of AS by studying the role of mesenchymal stem cells in the formation of osteoclasts in patients with ankylosing spondylitis. In this study, the fat mass and obesity-associated protein (FTO) levels of AS-MSCs and HD-MSCs were analyzed, and the role and mechanism of FTO in inhibiting the formation of osteoclasts in MSCs were explored by the detection of TRAP, F-actin, NFATc1 and CTSK. It was found that FTO, an enzyme responsible for removing methyl groups from RNA, was more abundantly expressed in MSCs in patients with as than in healthy donors. Studies have shown that decreasing FTO levels reduces the ability of MSCs to inhibit osteoclast development. Further experimental results showed that FTO affected the stability of the long non-coding RNA NORAD by changing its m6A methylation state. Inactivation of Lnc NORAD in MSCs significantly increases osteoclast formation by influencing mi R-4284, which can modulate MSC-mediated inhibition of osteoclast formation as reported in our previous studies. Finally, the increase of FTO level in AS-MSCs was revealed, and it was found that FTO regulates the function of AS-MSCs in inhibiting osteoclast formation through the Lnc NORAD/mi R-4284 axis. This may help elucidate the mechanisms of pathological osteogenesis and



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provide a potential therapeutic target for AS. However, there are still some minor issues that need to be addressed. 1. Has the change in the expression of osteoclast-related genes been verified in this study? 2. In animal experiments, is CT bone tissue scan performed to observe the changes of bone tissue? 3. Is there any osteoclast-related staining in animal tissue section staining experiments to verify the experimental results? 4. Have co-culture experiments been conducted to observe the inhibitory effect of normal and AS-derived bone marrow mesenchymal stem cells on osteoclasts? 5. Do the changes of inflammatory factors play a role in the differentiation and maturation of osteoclasts in AS disease?