ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2024 March 26; 16(3): 228-323

Published by Baishideng Publishing Group Inc

World Journal of Stem Cells

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World Journal of Stem Cells

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NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shengwen Calvin Li, Carlo Ventura

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https://www.wjgnet.com/1948-0210/editorialboard.htm

PUBLICATION DATE
March 26, 2024

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World J Stem Cells 2024 March 26; 16(3): 228-231

DOI: 10.4252/wjsc.v16.i3.228

ISSN 1948-0210 (online)

EDITORIAL

O-linked β-N-acetylglucosaminylation may be a key regulatory factor in promoting osteogenic differentiation of bone marrow mesenchymal stromal cells

Xu-Chang Zhou, Guo-Xin Ni

Specialty type: Cell and tissue engineering

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Naik D, India

Received: December 7, 2023
Peer-review started: December 7, 2023
First decision: January 29, 2024
Revised: February 2, 2024
Accepted: February 29, 2024
Article in press: February 29, 2024
Published online: March 26, 2024

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Abstract

Cumulative evidence suggests that O-linked β-N-acetylglucosaminylation (O-GlcNAcylation) plays an important regulatory role in pathophysiological processes. Although the regulatory mechanisms of O-GlcNAcylation in tumors have been gradually elucidated, the potential mechanisms of O-GlcNAcylation in bone metabolism, particularly, in the osteogenic differentiation of bone marrow mesenchymal stromal cells (BMSCs) remains unexplored. In this study, the literature related to O-GlcNAcylation and BMSC osteogenic differentiation was reviewed, assuming that it could trigger more scholars to focus on research related to O-GlcNAcylation and bone metabolism and provide insights into the development of novel therapeutic targets for bone metabolism disorders such as osteoporosis.

Key Words: O-GlcNAcylation; Osteogenic differentiation; Bone marrow mesenchymal stromal cells; Osteoporosis

Core Tip: O-linked β-N-acetylglucosaminylation (O-GlcNAcylation), an important post-translational modification of proteins, widely involved in the regulation of biological processes such as signal transduction and proteasomal degradation, plays an essential role in the initiation and progression of various diseases such as bone metabolism. In this study, we emphasized that maintaining appropriate levels of O-GlcNAcylation is beneficial for the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs). Insufficient or excessive levels of O-GlcNAcylation are detrimental to BMSC osteogenic differentiation.

Citation: Zhou XC, Ni GX. O-linked β-N-acetylglucosaminylation may be a key regulatory factor in promoting osteogenic differentiation of bone marrow mesenchymal stromal cells. *World J Stem Cells* 2024; 16(3): 228-231
URL: https://www.wjgnet.com/1948-0210/full/v16/i3/228.htm
DOI: https://dx.doi.org/10.4252/wjsc.v16.i3.228

INTRODUCTION

Bone marrow mesenchymal stromal cells (BMSCs), important precursors of osteoblastic lineage cells, are pluripotent stem cells with self-renewal, immunomodulatory, and multidifferentiation potentials[1]. As the major source of osteoblasts, BMSCs are important contributors to the bone tissue repair process. The abnormal osteogenic differentiation of BMSCs is an important cause of bone metabolism-related diseases, including osteoporosis[2,3]. O-linked β-N-acetylglucosaminylation (O-GlcNAcylation) is an important post-translational modification in which involves the attachment of a single O-linked N-acetylglucosamine (O-GlcNAc) moiety to Ser or Thr residues of cytoplasmic, nuclear, and mitochondrial proteins. O-GlcNAcylation can regulate fundamental cellular processes ranging from gene transcription and translation to protein localization, interaction, and degradation[4]. The donor for O-GlcNAcylation is a nucleoside sugar, such as uridine diphosphate GlcNAc (UDP-GlcNAc). UDP-GlcNAc, a key metabolite produced by the hexosamine biosynthetic pathway, is synthesized by consumption of uridine triphosphate, glucose, glutamine, and acetyl-CoA[5]. As a ubiquitous post-translational modification of proteins, O-GlcNAcylation is regulated by two conserved enzymes: O-GlcNAc transferase (OGT), which can add O-GlcNAc to proteins, and O-GlcNAc enzyme (OGA), which can remove O-GlcNAc from proteins. O-GlcNAcylation maintains optimal homeostatic balance through mutual regulation of OGT and OGA[4]. However, uncoupled OGT and OGA homeostasis have been shown to be associated with the pathogenesis of multiple human diseases, including bone metabolic diseases. Emerging evidence shows that O-GlcNAc modification is closely related to the osteogenic differentiation of BMSCs[6].

BMSCs have the potential to differentiate into osteoblasts, adipocytes, and chondrocytes[7,8]. A recent study showed that OGT knockout in mouse BMSCs inhibited bone formation while promoting bone marrow adipogenesis[9] , indicating that O-GlcNACylation may be a key regulatory factor affecting the differentiation fate of BMSCs. Runt-related transcription factor 2 (RUNX2) is a member of the polyomavirus enhancer-binding protein 2/core-binding factor superfamily[10,11]. The balance between osteogenesis and adipogenic differentiation in BMSC is coordinated regulated by transcription factors Runx2 and CCAAT/enhancer-binding protein beta (C/EBPβ) through O-GlcNAc post-translational modifications. The increased O-glycosylation of Runx2 is not only critical for osteogenic differentiation, but also promotes B lymphocytes by activating interleukin-7. Knockdown of OGT can activate the transcriptional activity of C/EBPβ to promote the adipogenic differentiation of BMSCs[12,13], and upregulate the expression of myelopoietic stem cell factor encoded by the Kitl gene, thereby increasing myopoiesis[14-17]. In addition, Kim *et al*[6] observed that elevated protein O-GlcNAc modification enhances the binding of Runx2 to Ose2 by promoting the transcriptional activity of Runx2 and inducing an increase in the expression of the osteoblast-specific marker osteocalcin (OCN)[18-21]. Another study reported that the osteogenic differentiation marker bone morphogenetic protein 2/7 reduced OGA activity[18]. During osteogenic differentiation process of BMSC, the overall level of O-GlcNACylation increases. Pharmacological inhibition of OGA promotes the expression of osteogenic differentiation makers, including alkaline phosphatase (ALP), OCN, and bone sialoprotein[6,18,22,23].

Hyperglycemia is reported to be closely related to bone formation inhibition and is a major factor in diabetic osteoporosis[24-27]. Previous studies have shown that high blood sugar levels increase the O-GlcNAcylation of proteins. Abnormal regulation of O-GlcNAcylation is closely associated with the pathogenesis of diabetes mellitus[28]. Therefore, hyperglycemia-induced excessive and abnormal O-GlcNAcylation may lead to reduced osteogenic differentiation and diabetic osteoporosis. Gu *et al*[29] demonstrated that excessive O-GlcNAcylation induced by high glucose, glucosamine, or GlcNAc treatment or OGT overexpression can reduce the expression levels of osteoblast markers, such as ALP, type I collagen, OCN, Runx2, and osterix, thereby inhibiting osteogenic differentiation. These results are consistent with the phenotypic reduction in bone formation observed in patients with type 2 diabetes. However, other studies have shown that the upregulation of O-GlcNAcylation through supplementation with OGA inhibitors promotes osteogenic differentiation and increases Runx2 transcriptional activity and matrix mineralization[6,18]. One explanation for aforementioned difference is that the effects of metabolic treatment (high concentration glucose treatment) and drug treatment (OGA inhibitors) may be different. Pharmacological inhibition of OGA increases the O-GlcNAcylation level by breaking the dynamic on/off cycle, whereas metabolic treatment or OGT overexpression increases the O-GlcNAcylation level by shifting the balance toward modification[30].

CONCLUSION

The osteogenic differentiation of BMSCs requires a moderate increase of O-GlcNAcylation, and an excessive increase in overall O-GlcNAcylation may inhibit the osteogenic differentiation of BMSCS. Therefore, the overall O-GlcNAcylation level should be maintained within an optimal range to protect normal cellular functions. The precise regulation of O-GlcNAcylation may be an effective strategy for promoting the osteogenic differentiation of BMSCs, correcting abnormal bone metabolism, and preventing bone-related diseases. Further elucidation of the potential regulatory mechanism between O-GlcNAcylation and the osteogenic differentiation of BMSCs will help to better understand the pathogenesis of bone metabolic diseases and provide novel ideas for the treatment and prevention of bone metabolic diseases.

FOOTNOTES

Author contributions: Zhou XC and Ni GX designed and coordinated the study; Zhou XC wrote the manuscript; and all authors approved the final version of the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Yuan YY

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