Early immunomodulation by magnesium ion: catalyst for superior osteogenesis

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http://doi.org/10.12336/biomatertransl.2023.04.009

How to cite this article: Li, B. Early immunomodulation by magnesium ion: catalyst for superior osteogenesis. *Biomater Transl.* **2023**, *4*(4), 294-296.

The bioactive ion, magnesium ion (Mg^{2+}), serving as a vital factor in promoting osteogenesis, has received a decade-long of attention and research.[1, 2] Over the past decades, numerous works have revealed the positive effects of Mg^{2+} on osteogenesis, and the underlying mechanisms were also investigated in detail. For instance, numerous researchers attribute the positive effects of Mg^{2+} on osteogenesis to its immunomodulatory property, which hastens the transition of pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype of macrophages, consequently enhancing osteogeneis.[3, 4] Additionally, Zheng et al.[5] discovered alternative mechanisms through which Mg^{2+} promotes osteogeneis. They elucidated that Mg^{2+} elevates neuronal calcitonin gene-related polypeptide-a levels in the femoral peripheral cortex and the ipsilateral dorsal root ganglia, which, in turn, leads to calcitonin receptor-like receptor- and receptor activity-modifying protein 1-dependent activation of cyclic adenosine monophosphate-responsive element binding protein 1 and osterix, ultimately enhancing the osteo-differentiation of isolated rat stem cells. This work offers valuable insights into the effect of Mg^{2+} in accelerating calcitonin gene-related polypeptide-a-mediated osteo-differentiation, shedding light on the therapeutic potential of Mg^{2+} in bone injury, especially in addressing special pathologic conditions like osteoporosis. Nevertheless, detrimental effects on osteogenesis of Mg^{2+} released upon degradation of Mg-based implants also have been detected.[6, 7] These contradictory outcomes may stem from an imprecise understanding of the multifaceted roles of Mg^{2+} in the intricate biological process of bone healing, suggesting the possibility that different types of cells engaged in various phases of bone formation may respond to Mg^{2+} in distinct ways.

Reporting in *Nature Communications*, Qiao et al.[8] provide a detailed investigation into the effects and the underlying biological mechanism of Mg^{2+} on immunomodulatory osteogenesis, with a special focus on its dose- and time-dependent behaviour. Transient exposure to Mg^{2+} during the first week at an artificial defect in the distal end of rat femora results in significant increases in trabecular bone fraction, trabecular number, bone mineral density and trabecular thickness without compromising the mechanical properties of the new bone when compared to both the control group without Mg^{2+} exposure and the sham group. Meanwhile, in the Mg^{2+} exposure group, a decrease in the number of osteoclasts was observed on day 56. Conversely, the enhanced role of Mg^{2+} in osteogenesis is attenuated when exposure is delayed to the 2nd week, even at the same dose. Furthermore, continuous Mg^{2+} delivery over the initial 2 weeks post-injury shows no differences in bone formation between Mg^{2+} treatment group and the group without Mg^{2+} exposure. Based on these findings, it appears that Mg^{2+} boosts osteogenesis when administered during the beginning stage of bone formation, while extended treatment seems to have detrimental effects on bone formation.

The authors attribute the time-dependent modulatory effects of Mg^{2+} on osteogenesis to its modulation of macrophages. Concretely, extracellular Mg^{2+} significantly promotes the activities of monocytes and their maturation into macrophages, and the enhanced effects positively correlate to the concentration of extracellular Mg^{2+}. More importantly, extracellular Mg^{2+} facilitates the upregulation of genes encoding cytokines in monocytes-derived macrophages that favour osteogenesis, including C-C motif chemokine ligand 5, interleukin (IL)-1 receptor antagonist, IL-8, transforming growth factor-β1, bone morphogenetic protein 2, vascular endothelial growth factor A, IL-10, and the downregulation of genes encoding cytokines that favour osteoclastogenesis, such as oncostatin M, IL-6, IL-1β, tumour necrosis factor α. It is because that extracellular Mg^{2+} contributes to

the elevated expression of the transient receptor potential cation channel member 7, and triggers a transient receptor potential cation channel member 7-dependent Mg^{2+} influx in macrophages. This process results in the cleavage and nuclear accumulation of transient receptor potential cation channel member 7-cleaved kinase fragments, which leads to the phosphorylation of Histone H3, giving rise to the transition of macrophage into a pro-osteogenic phenotype. Sequentially, IL-8 secreted by macrophages predominantly enhances the osteogenic effect when it appears within the first week of culture, while impairing the mineralisation process when present in the later stages of osteo-differentiation. Noticeably, the enhanced role of Mg^{2+} exposure in the osteogenic behaviours of mesenchymal stem cells is more pronounced when mediated by macrophages, compared to its direct effect on mesenchymal stem cells. In addition, prolonged exposure to Mg^{2+} (3 days or more) leads to elevated expression of inhibitory-κB kinase-α and -β in macrophages to phosphorylate inhibitor of κB and translocate p65 into nuclear, thereby over-activing the nuclear factor kappa B signalling pathway. This upregulation promotes osteoclastic differentiation of macrophages, increasing the amount of tartrate resistant acid phosphatase positive cells, and hinders extracellular matrix calcification, ultimately compromising bone formation (**Figure 1A**). This work conducts an in-depth investigation into the effects of Mg^{2+} on immunomodulatory osteogenesis, unveiling an effective window for administrating Mg^{2+} to facilitate bone healing: emphasizing the greater significance of the initial inflammation stage over the subsequent active bone repair stage.

Progressively, in a follow-up study, the authors further discovered that divalent metal cations like Mg^{2+}, Zn^{2+}, and Cu^{2+} stimulate macrophages to secrete prostaglandin E2, which interacts with prostaglandin E2 receptor 4 in sensory nerves, promoting their sprouting and arborisation.[9] This behaviour, regulated through cyclic adenosine monophosphate-response element binding protein signalling, leads to a downregulation of sympathetic tone, giving rise to promoted osteogenesis and downregulated osteoclastogenesis in the injured bone (**Figure 1B**). This work elucidates how Mg^{2+} mediates osteogenic effects through the interplay between immunomodulation and neuroregulation.

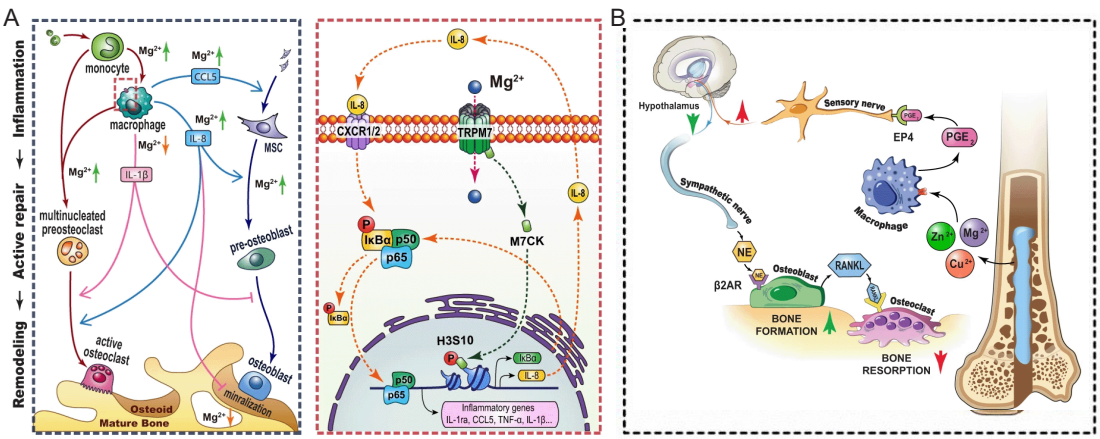

Figure 1. (A) Schematic illustration showing the mechanism by which Mg^{2+} regulates both macrophages and mesenchymal stem cells in the bone remodeling process. Reprinted from Qiao et al.[8] (B) schematic illustration showing the interplay between Mg^{2+} induced immunomodulation and central neuroregulation. Reprinted from Qiao et al.[9]

More generally, Mg plays an enhanced role in osteogenesis; however, optimising the ideal administration window is crucial for maximising its effectiveness and achieve greater efficiency. Simultaneously, the enhanced osteogenetic mechanism of Mg^{2+} likely initiates through early immunomodulation, followed by a complex series of physiological processes, involving osteogenic differentiation of mesenchymal stem cells, osteoclastic differentiation of macrophages, central neuroregulation and more. These works provide great enlightening and guiding insights, reminding researchers to bear in mind the balance between the osteo-enhancing and -impairing effects of Mg^{2+} exposure when utilizing Mg-based orthopaedic implants. Crucially, delving into the cross-talk between inflammation responses triggered by divalent metal cations and the subsequent physiological processes can potentially spark innovation in orthopaedic biomaterials infused with bioactive metal cations for advanced bone tissue engineering.

It is also needed to point out that recent works on the immunomodulatory osteogenic effects of Mg^{2+} have primarily concentrated on its regulation of innate immune responses, such as macrophage polarisation.[3, 4, 8, 9] Nevertheless, the adaptive immune system, particularly T cells, also holds significant sway in maintaining bone homeostasis.[10, 11] However, until now, the regulatory effects and underlying mechanism of Mg^{2+} on the adaptive immune system, as well as its subsequent cross-talk with osteogenesis-related cells have not been explored. Hence, it is expected that the upcoming studies will unveil these associated effects and mechanisms, further maximising the osteogenic effects of orthopaedic implants through the controlled release of bioactive ions.

Author contributions

BL: Conceptualization, investigation, and writing-review & editing. The author read and approved the final version of the manuscript.

Financial support

None.

Acknowledgement

The work was supported by the Shaanxi Province Natural Science Research Program, Nos. 2023YBSF194, 2023LLQY44; State Key Laboratory of Solidification Processing in NWPU, No. SKLSP202313; and Sichuan Science and Technology Program, No. 2022NSFSC1966.

Conflicts of interest statement

None.

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Received: November 20, 2023
Revised: November 28, 2023
Accepted: December 5, 2023
Available online: December 28, 2023