Title: Bisphosphonate-based hydrogel mediates biomimetic negative feedback regulation of osteoclastic activity to promote bone regeneration

Authors: Zhuo Li[1], Gang Li[2], Liming Bian[1*]

Affiliations: [1]Department of Biomedical Engineering, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China. [2] Department of Orthopaedic and Traumatology, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China (* Correspondence)

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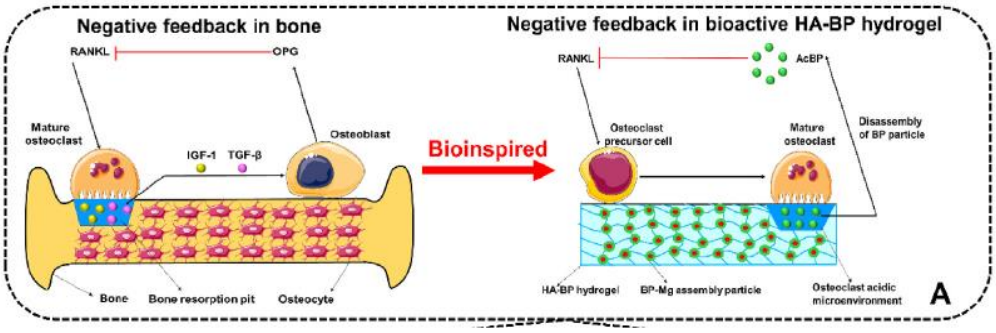
Background: Bone homeostasis is regulated by coupling bone resorption with bone formation, which is of great significance for the renewal of bone components, the repair of injury, and the maintenance of bone structure and mechanical properties. The intricate dynamic feedback mechanisms involved in bone homeostasis provide valuable inspiration for the design of smart biomaterial scaffolds to enhance in situ bone regeneration.

Methods: In this work, we assembled a biomimetic hyaluronic acid nanocomposite hydrogel (HA-BP hydrogel) by coordination bonds with bisphosphonates (BPs), which are antiosteoclastic drugs, and testes its effects on bone formation and bone resorption in vitro and in vivo.

Results: The HA-BP hydrogel exhibited expedited release of the loaded BP in response to an acidic environment. The in vitro studies showed that the HA-BP hydrogel inhibits mature osteoclastic differentiation of macrophage-like RAW264.7 cells via the released BP. Furthermore, the HA-BP hydrogel can support the initial differentiation of primary macrophages to preosteoclasts, which are considered essential during bone regeneration, whereas further differentiation to mature osteoclasts is effectively inhibited by the HA-BP hydrogel via the released BP. The in vivo evaluation in rat bone defect model showed that the HA-BP hydrogel can enhance the in-situ regeneration of bone.



Scheme shows the HA-BP hydrogel mediates negative feedback regulation of osteoclastic activity for enhanced bone regeneration.

Discussion and Conclusion: We demonstrated that the HA-BP hydrogel can support preosteoclast differentiation and its associated activity but inhibits subsequent osteoclast maturation from primary macrophages, thereby resulting in enhanced in-situ bone regeneration in vivo. The current work demonstrated a promising strategy to design biomimetic biomaterial scaffolds capable of regulating bone resorption and formation to promote bone regeneration.

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