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Perspective

Osteoimmunity-regulating biomaterials promote bone regeneration

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Osteoimmunomodulation is a fascinating approach for balancing osteoimmune through regulating reciprocal interactions between bone cells and immune cells [1]. Implantation of the osteoimmunity-regulating biomaterials regulates osteoimmune conditions in the host dynamically, thus intensifying osseointegration under physiological microenvironments [1]. This perspective presents a brief overview of osteoimmunity-regulating biomaterials for augmenting bone regeneration based on a recently published study by our research team [2].

Immune cells-based immune responses regulate the catabolism or anabolism of bone during the formation and remodeling phases, which occupy an essential position in different stages of bone regeneration [3]. Macrophages play an essential role in immune response, and immunomodulatory biomaterials indirectly affect bone repair by modulating the function of macrophages [2]. Macrophage recruitment is a major factor in triggering some local acute inflammation and brings a devastating catabolic effect on bone tissue. Notably, macrophages tactically differentiate into classically-activated M1 phenotype or pro-healing M2 phenotype, while the former produces pro-inflammatory cytokines to ruin adjacent bone, and the latter alleviates inflammation and/or enhances osteogenesis. Therefore, regulating macrophage polarization toward the M2 phenotype facilitates a reduction of inflammatory response in localized tissue, thus creating a beneficial immune microenvironment of bone.

We have recently developed a hierarchically biomimetic scaffold through integrating polylactide/hydroxyapatite (PLA/HA) matrix, gelatin methacryloyl (GelMA) hydrogel, manganese carbonyl (MnCO) nanosheet, and deferoxamine@poly(ε-caprolactone) nanoparticle (DFO@PCL NP) to augment bone regeneration by modulating the balance of bone metabolism and immune system (Scheme 1) [2]. Specifically, a three-dimensional (3D) printed scaffold was designed to mimic gradient structure characteristics in cancellous and cortical bone tissues; meanwhile, a favorable hydrogel was further infused into the scaffold

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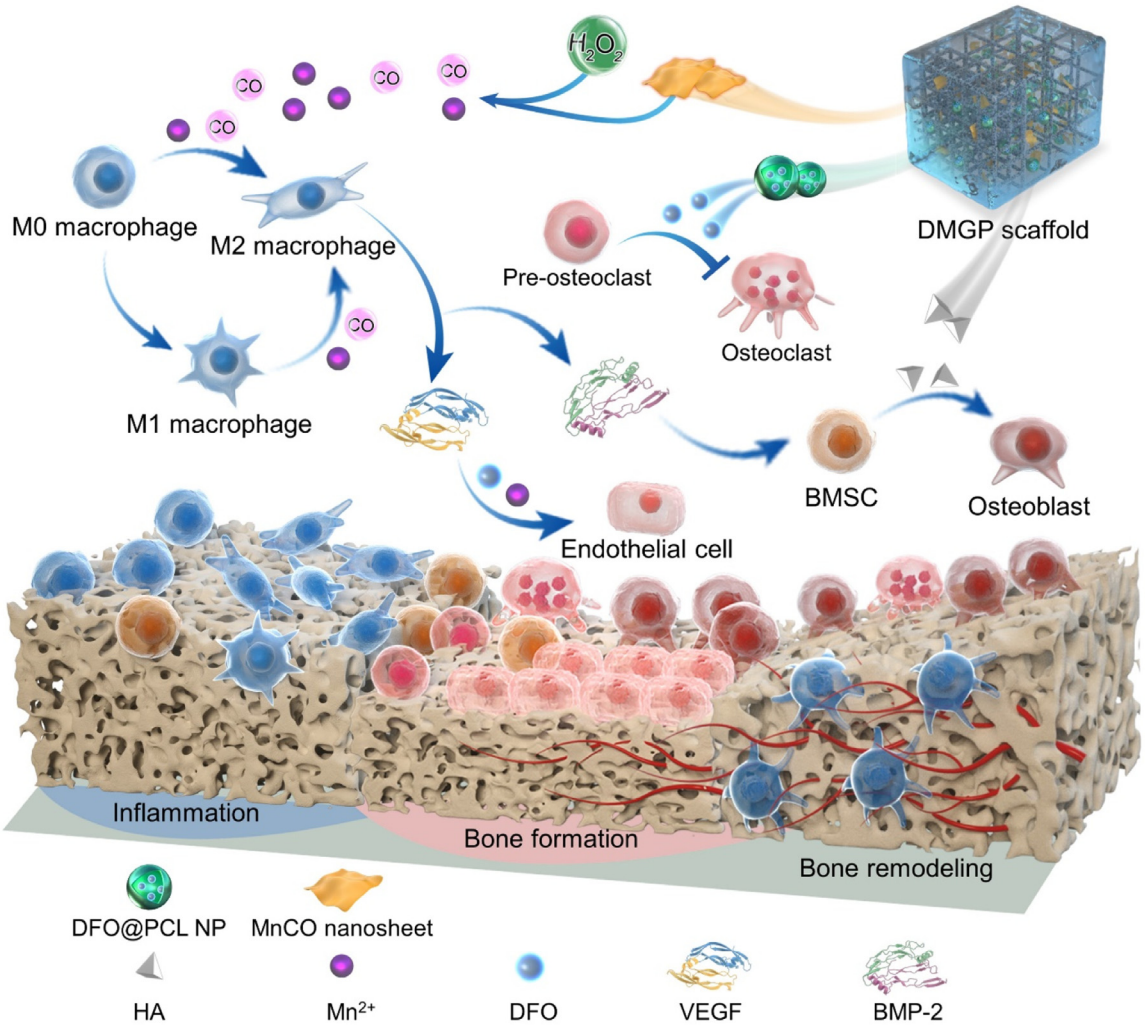

Scheme 1 – Osteoimmunity-regulating biomaterials for augmenting bone regeneration.
Abbreviations: BMP-2, bone morphogenetic protein-2; BMSC, bone marrow mesenchymal stem cells; DFO, deferoxamine; DFO@PCL NP, deferoxamine@poly(ε-caprolactone) nanoparticle; DMGP, DFO/MnCO@GelMA-PLA/HA; HA, hydroxyapatite; Mn^{2+}, manganese ion; MnCO, manganese carbonyl; VEGF, vascular endothelial growth factor.

to act as an extracellular matrix. Compared with other reported bone tissue engineering scaffolds, such hybrid DFO/MnCO@GelMA-PLA/HA (DMGP) scaffold owned the following advantages: (a) MnCO smartly released carbon oxide (CO) and manganese ion (Mn^{2+}) upon stimulation of an inflammatory microenvironment to alleviate inflammation through inducing macrophages to M2 phenotype significantly; (b) DFO@PCL NP, Mn^{2+}-activated hypoxia-inducible factor-1α (HIF-1α) pathway, and secreted vascular endothelial growth factor (VEGF) from M2 macrophages enhanced angiogenesis synergistically; (c) Promoted angiogenesis, osteoinductive ability of HA and bone morphogenetic protein-2 (BMP-2) from M2 macrophages, and suppression function of DFO on osteoclast differentiation further accelerated bone regeneration.

Immunofluorescence staining of the inflammatory genes showed that the DMGP scaffold possessed significant bone immunomodulatory function by effectively inhibiting the expression of tumor necrosis factor-α (TNF-α). Meanwhile, the amounts of $iNOS^+$ and $CD206^+$ cells in the region of bone defect were reduced and then increased after treatment with the MnCO-containing scaffold. It demonstrated that the DMGP scaffold effectively restrained inflammation and enhanced bone regeneration by transforming the macrophage phenotype from M1 to M2. Furthermore, DFO@PCL NP and MnCO nanosheet significantly enhanced the motility and migration ability of human umbilical vein endothelial cells (HUVECs) by initiating the transcription of cell migration genes. In addition, the DMGP scaffold exhibited an excellent pro-angiogenic effect by stimulating the transcriptional activity of HIF-1α and promoting VEGF expression in HUVECs [4,5].

Micro-computed tomography (micro-CT) and histopathological findings confirmed that bone defect was filled with numerous fibrotic tissue and granulomas in the blank group, with just a few newly-generated bone tissues appearing. In contrast, new bone tissues regenerated more rapidly in the DMGP group with excellent integration with the surrounding bone, ascribed to the following reasons. First, CO and Mn^{2+} induced M2 phenotype polarization of

macrophages, making a favorable local microenvironment for osteogenesis [2]. Besides osteoimmunomodulation, DFO and Mn^{2+} stabilized HIF-1α by interfering with or displacing ferrous iron in the catalyst to complementarily and synergistically achieve angiogenesis. Moreover, the sustained release of DFO and HA suppressed osteoclast differentiation and enhanced osteoblast response, thus improving bone reconstruction [5,6].

Although such DMGP scaffold exhibited favorable osteoinduction, osteoconduction, and osseointegration properties, some issues need further investigation. There may exist considerable differences in anatomical structures and microenvironmental compositions between various species and individuals of the same species. Therefore, many studies should be carried out on large animal models to expedite clinical translation of the DMGP scaffold. Additionally, this work lacked a detailed verification of the immunomodulation-related mechanism, and it is an urgent requirement to explore RNA sequencing to reveal the underlying molecular mechanisms of osteogenesis and immunomodulation.

In summary, an osteoimmunity-regulating bone tissue engineering scaffold was successfully fabricated to realize effective bone regeneration because of its strong immunomodulatory, angiogenic, and osteogenic abilities, demonstrating that such a unique scaffold with integrated biological functions put forward noteworthy enlightenment for large-scale bone defect repair.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2023.100774.

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