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REVIEW ARTICLE

Macrophages and bone inflammation

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Summary Bone metabolism is tightly regulated by the immune system. Accelerated bone destruction is observed in many bone diseases, such as rheumatoid arthritis, fracture, and particle-induced osteolysis. These pathological conditions are associated with inflammatory responses, suggesting the contribution of inflammation to bone destruction. Macrophages are heterogeneous immune cells and are polarized into the proinflammatory M1 and antiinflammatory M2 phenotypes in different microenvironments. The cytokines produced by macrophages depend on the macrophage activation and polarization. Macrophages and macrophage-derived cytokines are important to bone loss in inflammatory bone disease. Recent studies have shown that macrophages can be detected in bone tissue and interact with bone cells. The interplay between macrophages and bone cells is critical to bone formation and repair. In this article, we focus on the role of macrophages in inflammatory bone diseases, as well as discuss the latest studies about macrophages and bone formation, which will provide new insights into the therapeutic strategy for bone disease.

The translational potential of this article

Bone homeostasis is closely relevant to the immune system, which has raised an important field termed osteoimmunology. As one of the first lines of defence of the innate immune response, macrophages play a crucial role in bone integrity in physiological conditions and bone turnover in pathological conditions. During inflammation, macrophages are activated and produce a great amount of cytokines to affect bone formation and bone resorption. In light of this, a better understanding of the mechanisms by which macrophages regulate bone metabolism is essential for targeting macrophages as a therapeutic strategy in inflammatory bone diseases.

Introduction

Bone is a major component that makes up the skeleton of vertebrates. It is the strongest tissue in the body, and

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supports the body, protects the organs, and stores minerals. Apart from its structural function, bone also possesses metabolic functions. Bone metabolism is a lifetime process which is necessary to preserve structural integrity and maintain mineral homeostasis. This process involves osteoblastic bone formation and osteolytic bone resorption [1]. Bone formation refers to the building of new bone material by osteoblasts. Bone resorption is the process of breaking down bone and releasing the minerals by osteoclasts. The balance between bone formation and bone resorption is tightly controlled by osteocytes, immune cells, and the endocrine system.

Osteocytes, derived from osteoblasts, are the most common cells in bone. They are distributed in the mineralized bone matrix or on the surface of bone, and form an interconnected network with osteoblasts, osteoclasts, and the bone marrow. As a result, osteocytes possess the most potent ability to regulate bone metabolism through direct cell—cell contacts and the release of soluble molecules [2]. Receptor activator of nuclear factor kappa-β ligand (RANKL) is the key regulator for osteoclast differentiation and bone resorption. Osteocytes express higher amounts of RANKL than osteoclasts *in vitro* [3]. An increasing number of studies have shown that osteocytes can promote osteoclastogenesis and bone resorption through the production of RANKL. Sclerostin, an inhibitor of bone formation, is mainly produced by osteocytes in the bone. PTH or mechanical stimuli can reduce the sclerostin production of osteocytes, leading to increased bone formation. In addition to RANKL and sclerostin, osteocytes also produce other molecules, including nitric oxide, transforming growth factor (TGF), and macrophage chemotactic factor-1, which help to regulate bone metabolism. These findings suggest that osteocytes are the central regulators of bone homeostasis [4].

It is well known that there is a close interrelationship between bone metabolism and the immune system. Bone loss can be seen in some inflammatory diseases, including rheumatoid arthritis (RA) and periodontitis. Osteoimmunology was developed to investigate the impact of the immune system on bone metabolism under physiological and pathological conditions. An increasing number of studies have suggested that osteoimmunology includes the interactions between osteoblasts and osteoclasts, lymphocytes and osteoclasts, and osteoblasts and hematopoietic cells. T cell-deficient mice are osteoporotic and show reduced osteoprotegerin (OPG) production [5]. Depletion of B cells results in bone loss in rats [6]. In addition to immune cells and bone cells, cytokines are important to regulate bone metabolism. Activated T cells can reduce bone resorption and stimulate bone formation through the production of interferon-γ (IFN-γ) or interleukin (IL)-17 [7,8]. RANKL plays an important role in osteoimmunology. Under physiological conditions, RANKL is necessary for lymph node development. During an inflammatory response, activated T and B lymphocytes can release RANKL, which binds to the receptor activator of nuclear factor kappa-β (RANK) receptor on osteoclast precursors and induces osteoclastogenesis [9]. OPG can inhibit the RANK-RANKL interaction. The increased ratio of RANKL/OPG always indicates osteoclast differentiation and bone resorption [10].

In addition to T and B cells, the role of macrophages in osteoimmunology has received intensive attention. Macrophages are innate immune cells that are responsible for immune surveillance and pathogen removal. Accumulative studies have suggested that macrophages are crucial for bone metabolism and bone tissue engineering. Osteoclasts are derived from the monocyte-macrophage lineage and have been identified as the resident macrophages of the bone (Figure 1). Macrophages can induce matrix mineralization *in vitro* and induce osteoblast differentiation *in vivo* [11,12]. Depletion of macrophages reduces the number of osteoblasts *in vivo*.

The present work will focus on how macrophages interact with bone cells and elucidate how macrophage polarization affects bone formation. Moreover, we will discuss the role of macrophages in inflammatory diseases of the bone.

Macrophages and bone formation

Macrophages are a highly heterogeneous population derived from the myeloid cell lineage. As essential effectors of the innate immune system, macrophages play a critical role in host defence and inflammation. Macrophages can be divided into resident and inflammatory macrophages [13]. Resident macrophages can be found in nearly all tissues, and they participate in tissue repair, immune surveillance, and homeostatic maintenance [14,15]. Inflammatory macrophages derive from monocytes and traffic via the bloodstream to inflammatory sites. In response to microenvironmental stimuli, macrophages (both resident and inflammatory macrophages) can be activated and acquire distinct functional abilities: proinflammatory M1 (classically activated macrophages) and antiinflammatory M2 (alternatively activated macrophages) (Figure 2) [16]. M1 macrophages have proinflammatory functions and participate in the host defence against pathogens [17]. When activated by IFN-γ, granulocyte macrophage colony-stimulating factor, or other toll-like receptor (TLR) ligands, M1 macrophages can produce proinflammatory cytokines, such as IL-1β, IL-12, tumour necrosis factor-α (TNF-α), and superoxide anions, and induce a Th1 immune response [18]. M2 macrophages contribute to tissue repair and resolution of inflammation. IL-4 and IL-13 can induce M2 macrophages. After activation, M2 macrophages can produce IL-10, IL-1 receptor type α, and TGF-β, which ensue the activation of the Th2 immune response and antiinflammatory functions [19]. Under normal conditions, most macrophages display an M2 phenotype, which helps to maintain tissue homeostasis [20]. In the early stage of inflammation, macrophages are activated and polarized to an M1 phenotype. These M1 macrophages produce nitric oxide and proinflammatory cytokines, which can lead to tissue damage. During the resolution of inflammation, macrophages are predominantly polarized to an M2 phenotype, which can suppress proinflammatory cytokine production, clear debris, and restore tissue homeostasis [21].

A mountain of evidence has suggested that both resident and inflammatory macrophages can influence bone formation. Osteoclasts have been traditionally viewed as the

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