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ScienceDirect
Osteoporosis and Sarcopenia 1 (2015) 81−91
http://www.elsevier.com/locate/afos

Review article

Communication between the skeletal and immune systems

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Received 29 June 2015; accepted 30 September 2015
Available online 5 November 2015

Abstract

In the last two decades, numerous researchers have focused on elucidating the relationship between the skeletal and immune systems with respect to their regulatory mechanisms. It has now become clear that osteoclasts are derived from the same myeloid precursor cells that can differentiate into macrophages and myeloid dendritic cells. In addition, bone and immune cells coexist in the common microenvironment of the bone marrow and are thus influenced by similar mediators. Discovery of a common regulatory mechanism via the receptor activator of nuclear factor kappa-B ligand (RANKL)−receptor activator of NF-κB (RANK)−osteoprotegerin (OPG) axis in both the bone and immune system has not only increased understanding of the fundamental processes of bone homeostasis but has further crystalized understanding of the definitive regulatory correlation between bone and immunity. Moreover, many of the soluble mediators produced by immune cells, including cytokines, chemokines, and growth factors, regulate the activities of osteoclasts and osteoblasts. This increased recognition of the complex interactions between the immune system and bone has led to the development of the interdisciplinary field of osteoimmunology. In this review, we summarize the characteristics of bone cells and the soluble mediators responsible for crosstalk between the skeletal and immune systems. A more complete appreciation of the interactions between immune and bone cells should lead to better therapeutic strategies for diseases that affect either or both systems.
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Keywords: Osteoimmunology; Osteoclasts; Osteoblasts; RANKL/RANK/OPG; Pro-inflammatory cytokines

1. Introduction

The skeletal system has long been regarded as a metabolically inert organ; however, it is now well known that bone remodeling is continuously and dynamically carried out in order to maintain bone function and homeostasis. Recent reviews have described findings in the new field of osteoimmunology regarding the relationship between the skeletal and immune systems and their overlapping regulatory mechanisms [1,2]. Bone provides a microenvironment that is critical for the development of immune cells that are derived from hematopoietic stem cells (HSCs) and influence the various cytokines produced by immune cells to determine the fate of bone cells. Indeed, bone is an ideal anatomic microenvironment for HSC maintenance and differentiation, and recent data show that osteoblasts, which are bone matrix-producing cells, regulate the development of the HSC niche, from which all blood and immune cells are derived. The regulation of bone by hematopoietic and immune cells produces a variety of physiological and pathological effects. In pathological conditions such as rheumatoid arthritis (RA) and inflammatory bowel disease, infiltrating lymphocytes and other mononuclear cells provide several key factors that influence bone metabolism by altering the balance between bone-forming osteoblasts and bone-resorbing osteoclasts. Whether or not these interactions also influence normal bone homeostasis had been unclear until the discovery of RANKL (also known as TNF-related

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Peer review under responsibility of The Korean Society of Osteoporosis.

http://dx.doi.org/10.1016/j.afos.2015.09.004
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activation-induced cytokine, TRANCE) expressed in activated T cells and subsequent elucidation of its role as a pivotal factor for osteoclastogenesis, which has provided critical evidence that a physiological relationship exists between the normal immune system and bone metabolism [3−5]. Here, we provide a brief description of the current understanding of bone cells (osteoclasts and osteoblasts) and the immune cell-derived factors that regulate these cells and affect bone metabolism.

2. Characterizations of bone cells

2.1. Osteoclasts

Osteoclasts originate from HSCs that can differentiate into macrophages and dendritic cells, and multinucleated giant cells that form via the fusion of mononuclear precursor cells [1,2], and have a unique capacity to efficiently resorb the bone matrix. It has been conclusively demonstrated that RANKL (also designated as TNFSF11) is an essential factor that controls osteoclastogenesis and bone resorption both *in vitro* and *in vivo*. Almost 20 years ago, four research groups independently discovered and alternatively named this factor as TRANCE, RANKL, osteoclast differentiation factor (ODF), and osteoprotegerin ligand (OPGL). The first two groups [3,6] demonstrated that TRANCE/RANKL and its receptor (TRANCE-R/receptor activator of NF-κB [RANK]) are expressed in activated T cells and dendritic cells, respectively, and that these receptor−ligand interactions promote dendritic cell function and survival. The second two groups [4,5] found that this cytokine is derived from bone marrow stromal cells (BMSCs) and is an essential factor for *in vitro* osteoclastogenesis. These findings demonstrated that both the immune and skeletal systems share the common RANKL/RANK/osteoprotegerin (OPG) signal axis, leading to the first concept establishing a functional connection between these systems. Since the discovery of RANKL, a number of reviews have been written that explain the molecular pathways regarding the maturation of osteoclasts from bone marrow precursors [1,5]. Therefore, we will here briefly describe recent progress on the identification of the bone marrow cell population as osteoclast precursors.

Mononuclear cells from the bone marrow, peripheral blood, and spleen can differentiate into osteoclast-like cells (OCLs) in various *in vitro* culture systems [1,3,4]. A portion of the cell population from the murine bone marrow that did not express Sca-1, but was positive for CD117/c-kit was identified as osteoclast progenitors [2]. These cells produced tartrate-resistant acid phosphatase (TRAP)-positive OCLs via culture in semi-solid media or in co-culture with ST2 stromal cells after treatment with 1α,25-$(OH)_2$ vitamin D_3. Arai et al. [7] found that when c-kit-positive murine bone marrow cells were cultured with ST2 stromal cells, RANKL, and macrophage colony-stimulating factor (M-CSF), this cell population could differentiate into OCLs. These authors concluded that bone marrow cells expressing c-kit, c-fms, and $CD11b^{low}$ contained multipotent progenitor cells that frequently produce osteoclasts. This cell population did not initially express RANK (the receptor for RANKL), but its expression was induced following M-CSF treatment. Interestingly, in methycellulose culture, these progenitor cells differentiated into macrophages and mononuclear $TRAP^{+}$ cells, indicating their multipotent ability. Subsequently, osteoclast precursor cells were identified to be $CD3^{-}$, $CD45R^{-}$, and negative or low for CD11b expression, but positive for c-fms expression [2,8]. According to the expression of c-kit, this population of bone marrow cells was further separated into two categories. The first, $c\text{-}kit^{high}$ cells rapidly formed OCLs *in vitro* when cultured with M-CSF and RANKL, and the second, c-kit ^{low} or $c\text{-}kit^{-}$ cells slowly formed OCLs *in vitro*. This population of osteoclast precursors transiently expressed CD11b *in vitro*. Initially, the population of c-kit ^{low} or $c\text{-}kit^{-}$ cells efficiently produced OCLs; however, this cell population transiently formed $CD11b^{high}$ mononuclear osteoclast precursors following M-CSF and RANKL induction, and the expression of this antigen disappeared in multinucleated cells [2].

Human and murine cells that express an early marker of the myeloid dendritic cell lineage were found to differentiate into osteoclasts *in vitro*, indicating that there is some connection between osteoclasts and professional antigen-presenting dendritic cells [9]. In addition, it was shown that murine bone marrow-derived and splenic $CD11c^{+}$ dendritic cells, which are activated by cytokines and can present antigens to T lymphocytes, developed into osteoclasts under M-CSF and RANKL treatment [10]. Moreover, immature dendritic cells were found to be able to differentiate into OCLs in response to M-CSF and RANKL *in vitro*; however, neither mature myeloid dendritic cells nor plasmacytoid dendritic cells formed OCLs in culture [11]. This transdifferentiation was stimulated by pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α), and was inhibited by the addition of interferon (IFN)-α as well as IL-2, IFN-γ, and IL-4. It was previously suggested that macrophages, osteoclasts, and myeloid dendritic cells can differentiate from common progenitor cells [9], and single-cell clones from mouse bone marrow progenitor cells that are specific for macrophages and resident spleen dendritic cells *in vivo* also differentiated into these cells following treatment with the cytokines M-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) *in vitro* [12]. Recently, more conclusive results were reported with regards to the common progenitor cells for osteoclasts, macrophages, and antigen-presenting dendritic cells at the single-cell level [13]. Among the murine bone marrow cells expressing $B220^{-}CD3^{-}CD11b^{-/low}$ $CD115^{+}$ and either $CD117^{high}$, $CD117^{intermediate}$, or $CD117^{low}$, which have high osteoclastogenic potential, the population with a higher CD117 expression level was able to generate osteoclasts, macrophages, and dendritic cells *in vitro* with efficiencies of over 90%. In addition, cells with osteoclastogenic potential were also found in the blood and peripheral hematopoietic organs. However, the relationship between the bone marrow and peripheral monocyte progenitors remains unclear. In addition to the bone marrow, circulating osteoclast precursor cells expressing CD11b in the blood were identified, and proliferation of these precursors was stimulated by inducing an

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