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Crosstalk between bone niche and immune system: Osteoimmunology signaling as a potential target for cancer treatment

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ABSTRACT

There is a well recognized link between the bone and the immune system and in recent years there has been a major effort to elucidate the multiple functions of the molecules expressed in both bone and immune cells. Several molecules that were initially identified and studied in the immune system have been shown to have essential functions also in the bone. An interdisciplinary field embracing immune and bone biology has been brought together and called "osteoimmunology".

The co-regulation of the skeletal and immune systems strikingly exemplifies the extreme complexity of such an interaction. Their interdependency must be considered in designing therapeutic approaches for either of the two systems. In other words, it is necessary to think of the osteoimmune system as a complex physiological unit. Denosumab was originally introduced to specifically target bone resorption, but it is now under evaluation for its effect on the long term immune response. Similarly, our current and still growing knowledge of the intimate link between the immune system and bone will be beneficial for the safety of drugs targeting either of these integrated systems. Given the large number of molecules exerting functions on both the skeletal and immune systems, osteoimmunological understanding is becoming increasingly important. Both bone and immune systems are frequently disrupted in cancer; and they may be crucial in regulating tumor growth and progression. Some therapies – such as bisphosphonates and receptor activator of NF-κB ligand (RANKL) targeted drugs – that aim at reducing pathologic osteolysis in cancer may interact with the immune system, thus providing potential favorable effects on survival.

Introduction

Accumulating evidence over the past decade suggests a model of extensive interaction between immune system and bone. It has recently been found that this complex connection plays an important role also in cancer growth and spread to the skeletal system and, in turn, that tumor cells can alter and disrupt both immune and bone systems.

Interaction between the bone and the immune systems occurs both in physiologic and pathologic conditions: osteoclastogenesis and hematopoiesis take place in the bone marrow. Immune cells and bone cells have common precursors: cytokines, receptors, adaptor proteins, signaling molecules and transcriptional factors are shared by both systems [1]. Osteoimmunology" can be defined as a multidisciplinary area of research focusing on the molecular understanding of the complex interplay between bone and immune system. Many steps forward were made thanks to the discovery of the Receptor Activator of NF-κB (RANK)/RANK Ligand (RANKL)/Osteoprotegerin (OPG) system in the mid-1990s [2]. RANK/RANKL/OPG pathway plays a critical role in regulating osteoclastogenesis; in addition, it greatly influences immune,

Abbreviations: RANK, activator of NF-κB; RANKL, RANK ligand; OPG, osteoprotegerin; TRANCE, TNF-related activation-induced cytokine; TNF, tumor necrosis factor; IL, interleukin; DC, dendritic cell; DTCs, disseminated tumor cells; SREs, skeletal-related events; ZOL, zoledronic acid; TRAIL, TNF related apoptosis inducing ligand.

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cardiovascular, endocrine, and nervous systems. In particular, RANKL signaling affects the immune system by regulating antigen-specific immune responses and the interaction between T cells and dendritic cells, allowing the immune system to recognize and destroy abnormal cells and non-self antigens [3].

The RANK pathway biological function in osteoclastogenesis and immune system regulation is shown in Fig. 1. Recent studies in hematologic and solid malignancies indicate that targeting the bone microenvironment could have important therapeutic implications.

Moreover, currently available drugs – designed to reduce pathologic osteolysis that may occur in cancer – may interact with the immune system, with potential beneficial effects on survival. In this review, we discuss the essential role of signaling transduction pathways and transcription factors in bone and immune system. Also, we focus on the complexity and overlapping cellular and molecular interactions between the immune and bone systems.

RANK/RANKL/OPG pathway in bone and immunity

Physiological bone turnover requires a continuous interaction between osteoclasts and osteoblasts and the RANK/RANKL/OPG pathway plays a crucial role during the process of bone formation and resorption. RANK receptor is a type I membrane protein, mainly expressed on the surface of mature osteoclasts and their precursors, involved in their activation upon ligand binding, both in physiologic and pathologic conditions [4]. RANKL is a member of the tumor necrosis factor (TNF) cytokine family, a type-2 membrane-bound protein, expressed by stromal cells, osteoblasts, and immune cells or released in soluble form in the bone microenvironment [5]. RANKL, by binding RANK, induces osteoclast maturation, activation and survival. Under physiological conditions, RANKL/RANK pathway is antagonized by OPG, a soluble decoy receptor, member of the TNF superfamily, secreted by osteoblasts and osteogenic stromal stem cells, which competes with RANK for interaction with RANKL [6]. Hence, RANKL/OPG ratio is an important determinant for bone mass and skeletal integrity and enables the continuous remodeling of the bone matrix [7]. The critical role of RANKL/RANK pathway in osteoclastogenesis is demonstrated by experimental studies showing that knockout mice lacking either RANK or RANKL developed osteopetrosis due to the absence of bone resorption [8]. Expression of RANKL by osteoclastogenesis-supporting cells occurs in response to osteoclastogenic factors, such as parathyroid hormone, interleukin (IL)-1, IL6 and TNFα [9]. RANK signal transduction is mediated by TNF receptor-associated factors (TRAFs), in particular TRAF6, which activates PI3K, c-Src, Akt/PKB and mTOR among others, and subsequently different transcription factors including NF-κB [10,11]. TRAF6 seems to play a critical role in osteoclast as well as in dendritic cell (DC) maturation and activation. Moreover, RANKL stimulation activates reactive oxygen species (ROS) production, which are supposed to be important second messengers during osteoclastogenesis [12]. The dysregulation of the physiological equilibrium in the RANK/RANKL/OPG pathway leads to the pathological remodeling associated with cancer and to the development of bone metastasis. Tumor cells release growth factors and/or cytokines into the bone microenvironment, thus stimulating the production of RANKL from osteoblasts. RANK stimulation by RANKL leads to the differentiation of preosteoclasts into active osteoclasts, with resorption of the mineralized bone matrix, which results in releasing factors promoting colonization and tumor growth [13]. Hence, the RANK/RANKL/OPG pathway constitutes an important target for the treatment of cancer bone metastasis.

In addition to its biological function in osteoclastogenesis, RANK–RANKL–OPG signaling plays an important role in the development and regulation of the immune system as summarized in Table 1. Indeed it is essential in lymph-node organogenesis, in T and B lymphocyte development and in T cell self tolerance induction (along with CD40L-CD40) [14,15]. In addition, RANKL, mainly expressed on activated CD4+ and CD8+ T cells, may directly stimulate lymphocytes and DC survival, proliferation and function [10,16]. Moreover, autocrine RANKL/RANK signaling seems to play

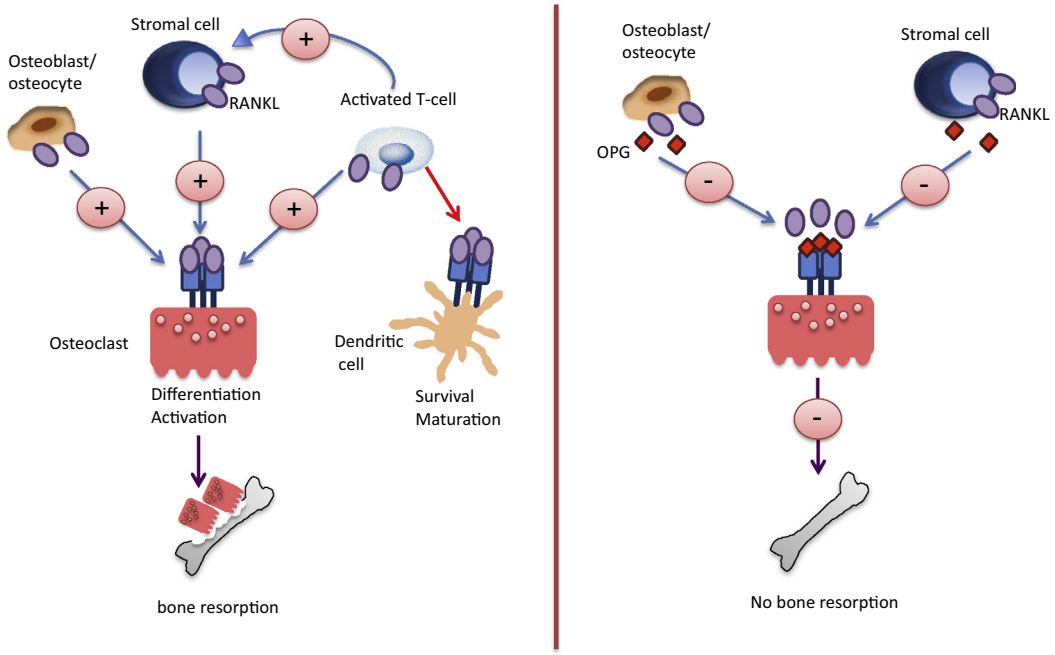

Fig. 1. RANKL is found on the surface of stromal cells, osteoblasts, and T cells. The interaction between RANKL and its receptor regulates osteoclast differentiation and activation both normally and in a variety of pathologic conditions associated with increased bone resorption, as rheumatoid arthritis. Indeed activated T lymphocytes expressing RANKL promote osteolysis directly, and indirectly by stimulating stromal cells. OPG, secreted by osteoblasts and osteogenic stromal stem cells, protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from interacting with RANK. RANK is also expressed on dendritic cell surface, facilitating their survival and maturation. RANK = receptor activator of nuclear factor kB; RANKL = RANK ligand; OPG = osteoprotegerin.