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Review

Tumor–host cell interactions in the bone disease of myeloma

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ABSTRACT

Multiple myeloma is a hematological malignancy that is associated with the development of a destructive osteolytic bone disease, which is a major cause of morbidity for patients with myeloma. Interactions between myeloma cells and cells of the bone marrow microenvironment promote both tumor growth and survival and bone destruction, and the osteolytic bone disease is now recognized as a contributing component to tumor progression. Since myeloma bone disease is associated with both an increase in osteoclastic bone resorption and a suppression of osteoblastic bone formation, research to date has largely focused upon the role of the osteoclast and osteoblast. However, it is now clear that other cell types within the bone marrow, including cells of the immune system, mesenchymal stem cells and bone marrow stromal cells, can contribute to the development of myeloma bone disease. This review discusses the cellular mechanisms and potential therapeutic targets that have been implicated in myeloma bone disease.

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Introduction

Multiple myeloma is a fatal hematological malignancy that develops within the bone marrow microenvironment. Multiple myeloma is the second most common hematological malignancy and the American Cancer Society estimated that approximately 20,000 new multiple myeloma diagnoses and 10,800 myeloma deaths occurred in 2007 in the United States alone [1]. Myeloma is characterized by the uncontrolled clonal proliferation of malignant plasma cells within the bone marrow. A unique feature of multiple myeloma, in contrast to other hematological malignancies, is the development of a destructive bone disease, resulting in osteolytic bone lesions, bone pain, and pathological fractures. The

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majority of patients present with, or will develop, bone disease during the course of their myeloma. The bone disease is now recognized as an integral component of myeloma and a contributing factor in tumor progression.

Multiple myeloma, and other cancers that metastasize to the bone marrow, create an interdependent relationship between tumor cells and cells of the bone marrow microenvironment, which promotes both tumor growth and bone destruction [2]. This was initially described as a reciprocal relationship between tumor growth and osteoclastic bone resorption, whereby myeloma cells release "osteoclast activating factors" and in turn, resorbing bone promotes tumor growth and survival (Fig. 1A) [3,4]. It is now clear that myeloma cells interact with numerous cell types with the bone marrow microenvironment and all these interactions have the potential to contribute to the associated bone disease (Fig. 1B). In the normal bone marrow microenvironment, bone is constantly undergoing remodeling with a delicate balance between osteoclastic bone resorption and osteoblastic bone formation. Within the myeloma microenvironment, there is a dysregulation in normal remodeling that results in enhanced osteoclastic bone resorption and suppressed bone formation. Myeloma cells play an active role in altering the balance in this process. Importantly, recent research has shown that other cell types within the microenvironment may also contribute to the bone disease. This review considers our current understanding of the mechanism of development of osteolytic bone disease in multiple myeloma.

Increased osteoclastic bone resorption

It was early histomorphometric studies that showed that bone resorption was increased in patients with myeloma [5]. These studies demonstrated that the surface undergoing resorption is increased. Furthermore, studies have also suggested that the depth of individual remodeling sites may be increased. This is consistent with both increased numbers of osteoclasts, increased resorptive activity by individual osteoclasts, or both mechanisms occurring simultaneously [6]. The demonstration that osteoclastic resorption was increased resulted in efforts to identify the molecular mediators responsible.

Greg Mundy was the first to demonstrate that myeloma cells produced an 'osteoclast activating factor' [3,4]. The identity of this factor(s), for many years, remained elusive. Studies implicated a number of cytokines, including lymphotoxin, interleukin-1 and tumor necrosis factor-α. These studies were limited to providing evidence of expression of molecules in what were often cell lines, or isolated, cultured myeloma cells and there was little evidence of functional data to support a causal role. However, in the last decade, two pathways have been shown to play a fundamentally important role.

The ligand for receptor activator of NFκB (RANKL)

The discovery that RANKL plays a critical role in normal osteoclast formation and function lead to studies investigating its potential importance in the development of myeloma bone disease. Early studies demonstrated that RANKL expression was increased in the bone marrow of patients with myeloma [7,8]. Furthermore, myeloma cells decrease expression of osteoprotegerin (OPG), the decoy receptor, by stromal cells and osteoblasts [9]. Other studies demonstrated that myeloma cells themselves were able to express RANKL directly, suggesting that these cells have the ability to bypass the normal osteoblast-dependent induction of osteoclastogenesis [10,11]. Despite this, not all studies have observed expression of RANKL by myeloma cells. However, more recently, CD38++/CD45+ and CD138+ myeloma cells have been shown to express RANKL and induce osteoclast formation directly [12]. Furthermore, other cells within the bone microenvironment may also contribute to increased RANKL expression. For example, myeloma cells induce expression of RANKL in T cells, a process mediated by interleukin-7 production [13]. Irrespective of the cellular source of RANKL, serum levels are elevated and OPG levels decreased in patients with myeloma and this is associated with the development of bone disease [14].

The demonstration of increased RANKL expression in myeloma has resulted in studies investigating the effect of blocking RANKL in experimental models of myeloma. Recombinant OPG has been shown to inhibit osteoclastogenesis, prevent myeloma-induced bone loss and the formation of bone lesions in the 5T2MM murine model of

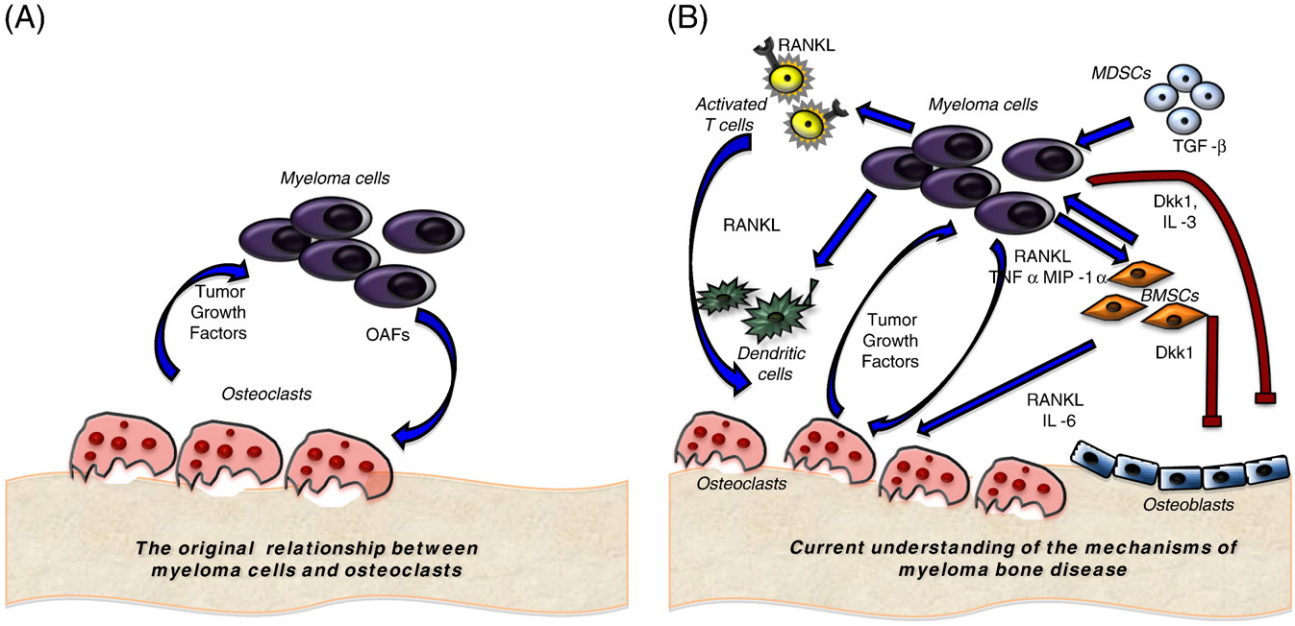

Fig. 1. Progression of our understanding of the complex cellular relationships in myeloma bone disease. (A) The original studies first described the relationship between myeloma cells and osteoclasts, whereby myeloma cells released "osteoclast activating factors" (OAFs) that stimulated osteoclastic bone resorption which in turn released growth factors which promoted myeloma cell growth and survival. (B) Our current knowledge has identified many more cell types and factors which contribute to disease progression, although the original concepts of tumor cells promoting bone destruction which in turn promotes tumor growth remain the fundamental aspects of this increasingly complex network of interactions.