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Myeloma bone disease: Progress in pathogenesis

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ABSTRACT

Myeloma bone disease (MBD) is one of the most serious complications of multiple myeloma (MM) and the most severe cause of MM morbidity. Dysregulation of osteoblast and osteoclast cells plays key roles in MBD. In the bone marrow microenvironment, myeloma cells, osteoblasts, osteoclasts and bone marrow stromal cells can secrete multiple cytokines, categorized as osteoclast cell activating factors (OAFs) and osteoblast cell inactivating factors, which have been discovered to participate in bone metabolism and contribute to the pathogenesis of MBD. Several signaling pathways related to these cytokines were also revealed in the MBD pathogenesis. To better understand the pathogenesis of MBD and therefore the potential therapeutic targets of this disease, we will summarize recent study progress in the factors and underlying signaling pathways involved in the occurrence and development of MBD.

Contents

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1. Introduction

Multiple myeloma (MM) is a malignant monoclonal plasma cell disease that accounts for 1% of all tumors and 10% of hematologic malignancies (Rajkumar et al., 2011). MM is characterized by malignant plasma cell hyperplasia, monoclonal immunoglobulin (M protein) in the serum and urine, which can lead to anemia, renal insufficiency, wide-spread bone lesions, hypercalcemia and serious recurrent infections. Despite of the substantial progress of treatments that significantly increase the response rate and prolong survival to a certain extent, MM is still incurable. Myeloma bone disease (MBD) is one of the most serious complications of MM (Walker et al., 2014). Approximately half to two third patients with MM come to the hospital because of the bone pain caused by MBD.

Normal physiologic bone environment is maintained by interaction and balance between osteoblast (OBs) and osteoclast cells (OCs). Recent researches showed that MBD is the outcome of imbalance of bone metabolism, in which bone absorption increases and bone construction decreases (Edwards et al., 2008; Silvestris et al., 2007). Further studies showed that dysregulation of OBs and OCs serves as the key process in the pathogenesis of MBD (Hameed et al., 2014). Increased OCs activity in MM patients will promote bone absorption, while suppression of OBs activity can lead to impaired bone formation. In the bone marrow microenvironment, besides OBs and OCs, myeloma cells (MCs) and bone marrow stromal cells (BMSCs) also can secrete various cytokines that participate in bone absorption and reconstruction solely or in combination, termed osteoclast cell activating factors (OAFs) and osteoblast cell inactivating factors (Oranger et al., 2013; Roodman, 2010) (Table 1). The pathogenesis of MBD depends primarily on the interaction of these two categories of factors, which are the main topics of this review. Some signaling pathways in myeloma cells were recently confirmed to be involved in the pathogenesis of MBD (Heusschen et al., 2016), which also will be reviewed in this article.

2. Increased bone absorption

Increased OC activity is one of the important mechanisms during the development of MBD (Nakashima et al., 2012). Mundy et al. (1974) found important OAFs in the myeloma cell culture medium, such as IL-6, IL-1β, TNFα and parathyroid hormone-related protein (PTHrP). In addition, the interactions between myeloma cells and the bone marrow microenvironment can also produce other OAFs (Terpos et al., 2014), such as macrophage inflammatory protein-1α (MIP-1α), receptor activator of nuclear factor-κB (RANK) and its ligand (RANKL), osteoprotegerin (OPG) and Annexin II. Some signaling pathways, such as Notch signaling, PI3K/AKT/mTOR signaling pathway, BDNF/TrkB, also play important roles in bone absorption.

2.1. RANKL/OPG

RANKL is a member of tumor necrosis factor (TNF) superfamily (Nakashima et al., 2011). It is encoded by the human chromosome 13q14 and mainly expressed on the surface of BMSCs and OBs. The expression of RANKL is regulated by a variety of cytokines and hormones (Sezer et al., 2003), such as parathyroid hormone, 1, 25-dihydroxyvitamin vitamin D_3 and prostaglandin E_2. After the specific binding between RANKL and RANK, their downstream

Table 1
Factors involved in myeloma bone disease.

Factors	Origin	Biological function
Osteoclastic activation		
RANKL	BMSCs and OBs	Major OC activation
MIP-1α	Macrophages and MCs	Chemotaxis activation in OC precursors
SDF-1α	BMSCs	Homing, migration of MCs and OC activation
VEGF	MCs	OC activation, IL-6 induction by stromal cells
OPN	OBs and OCs	Inflammatory responses, angiogenesis, apoptosis, and tumor metastasis
LIGHT	Immune cells	OC activation through NF-κB and JNK pathways
IL-6	BMSCs and MCs	Myeloma cell growth
PTHrP	MCs	Stromal cell stimulation
Annexin II	MCs	OC activation through RANKL/OPG
Exosomes	BMSCs	OC activation through PI3K/AKT pathway
MDSCs	Immature myeloid cells	OC activation through NO signaling pathway
Osteoblastic inhibition		
DKK1	BMSCs and OBs	Inhibition of Wnt pathway
sFRP-2	BMSCs and OBs	Inhibition of Wnt pathway
Runx2	BMSCs	Activation of OB differentiation and stromal cell maturation
TGF-β	BMSCs and OBs	OBs differentiation inhibition
IL-3	Marrow T cells	Stromal cell activation
IL-7	Marrow T cells	Inhibition of OB stimulation and maturation
HGF	MCs	Apoptosis activation inflammatory induction
MIP-1α	Macrophages and MCs	Inhibition of RUNX2 and Osterix
HPSE	MCs	Upregulation DDK1, Inhibition of Wnt pathway

RANKL: ligand of the receptor activating the nuclear factor κB; BMSC: bone marrow stromal cell; OB: osteoblast; OC: osteoclast; MIP: Macrophage inflammatory protein; MC: myeloma cell; IL: interleukin; VEGF: vascular endothelial growth factor; OPG: osteoprotegerin; MDSCs: Myeloid-derived suppressor cells; DKK1: Dickkopf-1; sFRP-2: secreted frizzled related protein-2; Runx2: Runt-related transcription factor 2; TGF-β: transforming growth factor-β; HGF: hepatocyte growth factor; HPSE: Heparanase.