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Biology and treatment of myeloma related bone disease

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ABSTRACT

Myeloma bone disease (MBD) is the most common complication of multiple myeloma (MM), resulting in skeleton-related events (SREs) such as severe bone pain, pathologic fractures, vertebral collapse, hypercalcemia, and spinal cord compression that cause significant morbidity and mortality. It is due to an increased activity of osteoclasts coupled to the suppressed bone formation by osteoblasts. Novel molecules and pathways that are implicated in osteoclast activation and osteoblast inhibition have recently been described, including the receptor activator of nuclear factor-kB ligand/osteoprotegerin pathway, activin-A and the wingless-type signaling inhibitors, dickkopf-1 (DKK-1) and sclerostin. These molecules interfere with tumor growth and survival, providing possible targets for the development of novel drugs for the management of lytic disease in myeloma but also for the treatment of MM itself. Currently, bisphosphonates are the mainstay of the treatment of myeloma bone disease although several novel agents such as denosumab and sotatercept appear promising. This review focuses on recent advances in MBD pathophysiology and treatment, in addition to the established therapeutic guidelines.

1. Introduction

Multiple myeloma (MM) is a relatively common hematological malignancy characterized by the accumulation of abnormal plasma cells in the bone marrow, the production of a monoclonal protein present in the blood or urine, and associated organ dysfunction presenting with osteolytic bone destruction, hypercalcemia, renal failure, anemia, and an increased risk for infections. Myeloma Bone disease (MBD), in the form of lytic lesions or osteopenia due to increased osteoclast activity, accompanied by suppressed osteoblast function is one of the devastating consequences of myeloma [1]. MM cells inhibit osteoblast differentiation and stimulate osteoclast function, resulting in bone resorption and consequent MBD. In turn, growth factors released by the increased bone resorptive process, also increase the growth of MM cells, creating a vicious cycle of tumor expansion and bone destruction. New insights into the pathophysiology have enhanced our understanding of myeloma cell growth and bone destruction. The biologic pathway of the receptor activator of nuclear factor-kappa B (RANK), its ligand (RANKL), and osteoprotegerin (OPG) which is the decoy receptor of RANKL is of major importance for the increased osteoclast activity observed in MM [2]. More recently, activin-A has been implicated in MM bone disease, through stimulating RANK expression and inducing osteoclastogenesis [3]. On the other hand, Wnt signaling pathway inhibitors, such as dickkopf-1 (DKK-1) and sclerostin, are important inhibitors of osteoblast function [4,5]. These insights will probably lead to better bone-directed therapies aimed at restoring bone homeostasis by targeting either osteoclast or osteoblast activity. This review summarizes the latest available data for the mechanisms of bone destruction in MM and novel agents targeting MBD. (See Fig. 1.)

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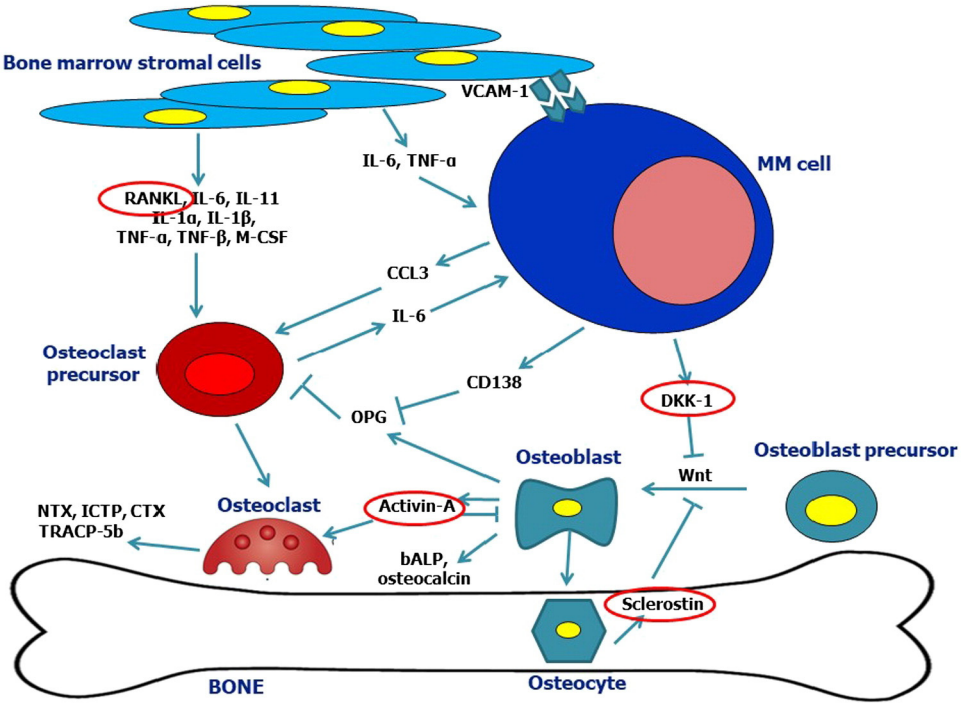

Fig. 1 – Schematic overview of myeloma bone disease pathophysiology. Novel therapeutic targets are highlighted.

2. Normal Bone Remodeling

Normal bone consists of a mineralized part and an organic part, made of collagen and non-collagen proteins. Osteocytes, osteoclasts, and osteoblasts maintain homeostasis in normal physiologic states by balancing bone formation and bone resorption. Osteocytes make up 90% to 95% of all bone cells, and osteoclasts and osteoblasts make up fewer than 10% [6]. Osteoclasts are multinucleated cells originating from hematopoietic stem cells committed to monocyte–macrophage lineage. They contain certain proteins, such as tartrate-resistant acid phosphatase (TRAP), tartrate-resistant trinucleotide phosphatase, carbonic anhydrase II, calcitonin receptors, and a few cathepsins (lysosomal proteases) [7], whose main function is bone resorption. Osteoblasts are mononuclear cells originating from mesenchymal stem cells. They contain the enzyme alkaline phosphatase, which is used as a marker of osteoblastic activity [8]. Their normal location is near the bone surface where new bone is laid down and their main function is bone formation, by collagen synthesis, osteocalcin production, and mineralization [9]. Osteoblasts that become a part of mineralized matrix are called osteocytes. Bone remodeling is a continuous process, consisting of old bone resorption (osteoclastic activity) and new bone formation (osteoblastic activity). This process is well balanced in a normal person to keep the bones in healthy form [10]. Osteocytes serve as the main regulators of bone homeostasis between osteoclasts and osteoblasts by secreting several cytokines that regulate the activity of these cells, such as sclerostin, DKK1, RANKL, and OPG [6].

Osteoclasts are regulating RANK, its ligand RANKL, and OPG signaling pathway. RANK-RANKL signaling activates downstream signaling pathways required for osteoclast development, differentiation, and maturation. RANK is a transmembrane signaling receptor, member of the tumor necrosis receptor superfamily, which is mainly expressed on the surface of osteoclast precursors, produced by bone marrow stromal cells (BMSCs), osteoblasts, and activated T-lymphocytes [11,12]. Its expression is induced by cytokines that stimulate bone resorption [13] such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D3 and prostaglandins [14,15]. Interestingly, apoptotic osteocytes express RANKL stimulating osteoclast differentiation [16] and recruiting them to sites of remodeling. The important role of RANKL in normal osteoclastogenesis has been clearly shown in RANKL or RANK gene knockout mice. These animals lack osteoclasts, and as result develop severe osteopetrosis [17–19]. OPG is a soluble decoy receptor for RANKL, member of the tumor necrosis factor receptor superfamily [20]. It is produced by osteoblasts, as well as BMSCs and blocks the interactions of RANKL with RANK, thereby limiting osteoclastogenesis. It is regulated by interleukin 1 beta (IL-1b), tumor necrosis factor alpha (TNF-a), transforming growth factor beta (TGF-b), estradiol and 17b-estriol. OPG-deficient mice develop severe osteopenia and osteoporosis [21–23]. In normal subjects, the RANKL/OPG ratio is very low. However, an abnormal RANKL/OPG ratio is found both in benign and malignant bone diseases [24].

Osteocytes also regulate osteoblasts by secreting sclerostin and DKK1, which block canonical Wnt signaling pathway via binding to low-density lipoprotein receptor–related proteins 5 and 6 (LRP5/LRP6) on the surface of osteoblasts [6]. Binding of Wnt glycoproteins to the Wnt receptor and its co-receptors LRP5/LRP6 leads to stabilization of β-catenin. In turn, β-catenin accumulates in cytoplasm,