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Review

Emerging molecules in the interface between skeletal system and innate immunity

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ABSTRACT

Despite the improved treatment of bone destruction, significant unmet medical need remains. For example, there is a limited benefit of continued bisphosphonate therapy for osteoporotic patients, and only minor populations of rheumatoid arthritis patients obtain biologic-free remission. Therefore, the identification of a novel therapeutic target for bone destructive diseases remains an important issue in the field of skeletal biology. To date there has been little progress in identifying osteo-innate-immunological regulators that could be used for the prophylactic treatment of inflammatory bone destruction. Recently, we identified several new molecules that are critical osteo-innate-immunological regulators by using gene targeting technology. These findings may offer an invaluable opportunity to regulate bone-destructive diseases, such as osteoporosis and rheumatoid arthritis.

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1. Introduction

Bone destructive diseases such as age-related osteoporosis and rheumatoid arthritis (RA) are serious diseases in developed countries [1]. To avoid spine and hip fractures in elderly patients, physicians choose continued bisphosphonate therapies [2]. The recent innovation of monoclonal antibody therapies has brought about the rapid progress of RA treatment [3,4]. Despite significant advances in the treatment of bone destruction, there is still a large unmet clinical need. For example, there is little clinical benefit of continued bisphosphonate therapy beyond 5 years for the prevention of osteoporotic fracture [2], and only limited populations of RA patients obtain drug-free remission. Therefore, understanding the molecular basis of bone metabolism and identification of prophylactic targets of bone destruction are still important in the field of geriatric medicine and rheumatology. Recently, accumulating evidence suggested that humoral factors from the innate immune system regulate osteoclastogenesis and bone formation[5]. The contribution of cytokines to the pathogenesis of bone destruction has been extensively characterized. In contrast, there have been few reports of anti-inflammatory factors produced by the bone

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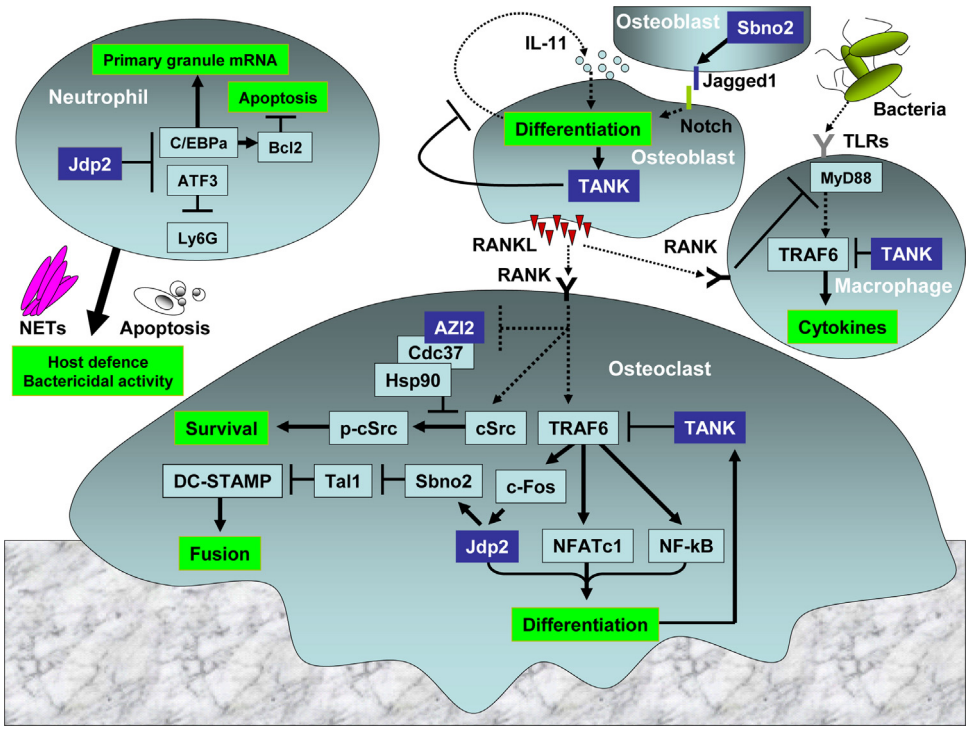

Fig. 1. Osteo-innate-immunological regulators. RANKL suppresses pro-inflammatory cytokine production. TANK suppresses pro-inflammatory cytokine production, osteoclastogenesis and bone formaion. AZI2 negatively regulates osteoclast survival. Jdp2 is critical for osteoclast and neutrophil differentiation. Sbno2 is critical for osteoclast fusion and bone formation.

metabolic system. Furthermore, there has been little progress in identifying intracellular molecules that regulate both the innate immune system and skeletal system (so-called "osteo-innate-immunological" regulators) that could be prophylactic targets for inflammatory bone destruction. Recently, we demonstrated that Receptor activator of nuclear factor kappa-B (NF-κB) ligand (RANKL), which is critical for osteoclast differentiation, protected mice from endotoxin shock [6]. We also reported several new molecules that are critical osteo-innate-immunological regulators both *in vivo* and *in vitro* using gene-targeted mice[7–10]. In this review, we focus on newly identified key molecules involved in inflammation and bone metabolism, and discuss their therapeutic potential.

2. RANKL is essential for osteoclastogenesis and inhibits inflammatory cytokine production

RANKL (also known as osteoclast differentiation factor, tumor necrosis factor (TNF)-related activation induced cytokine, or osteoprotegerin ligand) is a type 2 transmembrane ligand [11–13]. RANKL is expressed on bone-forming osteoblasts, which also secrete a soluble form RANKL. Osteoclasts are large multinucleate cells that originally differentiate from the myeloid lineage. Myeloid lineage cells express RANKL receptor RANK, and upon stimulation by RANKL, transcription factors such as NF-κB [14], cellular oncogene fos (c-Fos) [15,16], and nuclear factor of activated T cells are activated [17] to induce osteoclastogenesis. Other than RANKL, osteoblasts secrete osteoprotegerin (OPG), which blocks RANKL-RANK interactions [18,19]. The disappearance of osteoclastogenesis is observed in RANKL-deficient mice and this phenotype causes a lack of tooth eruption and bone marrow cavities [20]. In contrast to RANKL deficiency, OPG-deficient mice exhibit severe osteoporosis because of increased osteoclastogenesis [18,19]. To date, the RANKL-OPG axis has been mainly investigated in the context of skeletal homeostasis, but its role in pro-inflammatory cytokine production is not fully understood. We demonstrated that mouse serum contains soluble RANKL and OPG. When LPS or bacteria was injected intravenously into mice, OPG concentrations were dramatically up-regulated, but RANKL concentrations were impaired [6]. Importantly, RANKL-deficient mice exhibited increased proinflammatory cytokine production in response to lipopolysaccharide (LPS) and were highly susceptible to LPS-induced death. In contrast, OPG-deficient mice exhibited an impaired production of proinflammatory cytokines. Furthermore, prior injection of RANKL protected mice from LPS-induced death, suggesting that RANKL may have prophylactic potential for treatment of septic shock. Importantly, RANKL pretreated macrophages exhibited an impaired production of proinflammatory cytokines in response to bacteria, and this RANKL-induced tolerance was observed by pretreatment, even as short as 6 h. To gain insight into the mechanisms underlying RANKL-induced tolerance, we checked the expression levels of Toll-like receptor (TLR) signaling components, and revealed that MyD88, a critical adaptor protein of TLR signaling was significantly down regulated after the RANKL treatment [6]. Recently, it was reported that OPG-deficient mice or recombinant RANKL-treated mice exhibited impaired infarct volume and brain edema *via* reduced ischemic inflammation [21]. Furthermore, RANKL signaling attenuated inflammation through TLR signaling in microglia [21]. Collectively, these findings suggest that RANKL suppresses pro-inflammatory cytokine production in response to LPS and that RANKL can act as a prophylactic agent against septic or ischemic inflammation (Fig. 1 and Table 1).

3. TRAF family member-associated NF-κB activator (TANK) is a negative feedback regulator of osteoclastogenesis and bone formation

TLRs recognize bacteria and their components, and activate NF-κB to induce proinflammatory cytokines [22]. It is well established that tumor necrosis factor receptor-associated factor 6 (TRAF6)