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Natural products for treatment of bone erosive diseases: The effects and mechanisms on inhibiting osteoclastogenesis and bone resorption

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ABSTRACT

Excessive bone resorption plays a central role on the development of bone erosive diseases, including osteoporosis, rheumatoid arthritis, and periodontitis. Osteoclasts, bone-resorbing multinucleated cells, are differentiated from hemopoietic progenitors of the monocyte/macrophage lineage. Regulation of osteoclast differentiation is considered an effective therapeutic target to the treatment of pathological bone loss. Natural plant-derived products, with potential therapeutic and preventive activities against bone-lytic diseases, have received increasing attention in recent years because of their whole regulative effects and specific pharmacological activities, which are more suitable for long-term use than chemically synthesized medicines. In this review, we summarized the detailed research progress on the active compounds derived from medical plants with potential anti-resorptive effects and their molecular mechanisms on inhibiting osteoclast formation and function. The active ingredients derived from natural plants that are efficacious in suppressing osteoclastogenesis and bone resorption include flavonoids, terpenoids (sesquiterpenoids, diterpenoids, triterpenoids), glycosides, lignans, coumarins, alkaloids, polyphenols, limonoids, quinones and others (steroid, oxoxishhone, fatty acid). Studies have shown that above natural products exert the inhibitory effects via regulating many factors involved in the process of osteoclast differentiation and bone resorption, including the essential cytokines (RANKL, *M*-CSF), transcription factors (NFATc1, *c*-Fos), signaling pathways (NF-κB, MAPKs, Src/PI3K/Akt, the calcium ion signaling), osteoclast-specific genes (TRAP, CTSK, MMP-9, integrin β3, OSCAR, DC-STAMP, Atp6v0d2) and local factors (ROS, LPS, NO). The development of osteoclast-targeting natural products is of great value for the prevention or treatment of bone diseases and for bone regenerative medicine.

Contents

Abbreviations: MNCs, multinucleated cells; TRAP, tartrate-resistant acid phosphatase; RANKL, receptor activator of nuclear factor-κB ligand; *M*-CSF, macrophage colony stimulating factor; OPG, osteoprotegerin; *c*-fms, colony-stimulating factor-1 receptor; ERK, extracellular signal regulated protein kinases; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; TNF, tumor necrosis factor; TRAF6, TNF receptor-associated factor 6; NF-κB, nuclear factor-κB; MAPKs, mitogen activated protein kinases; JNK, *c*-jun-*N*-terminal kinase; NFATc1, nuclear factor of activated *T*-cells cytoplasmic 1; OSCAR, osteoclast-associated receptor; MMP-9, matrix metallopeptidase-9; OC-STAMP, osteoclast stimulatory transmembrane protein; DC-STAMP, dendritic cell-specific transmembrane protein; CTSK, cathepsin K; ICAM-1, intracellular adhesion molecule-1; Fosl1, Fos-like antigen 1; *c*-Src, *C*-terminal Src kinase; IκB, inhibitor κB; IKK, IκB kinase; BMMs, bone marrow-derived macrophages; CTR, calcitonin receptor; Atp6v0d2, d2 isoform of vacuolar (H^+) ATPase V0 domain; ROS, reactive oxygen species; PLCγ, phospholipase Cγ; PKC, protein kinase C; PGE2, prostaglandin E2; HIF-1α, hypoxia-inducible factor-1α.

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1. Introduction

Bone diseases, caused by bone loss and impaired bone quality, are a major health problem in the aging population and are associated with high morbidity and mortality. Bone homeostasis is dynamically regulated through the coordinated action of osteoclast-mediated bone resorption and osteoblast-induced bone formation [1]. Enhanced bone resorption by osteoclasts, which is not fully compensated by bone formation, is a critical mechanism in pathological bone diseases such as osteoporosis, rheumatoid arthritis, Paget's disease, periodontal disease, and multiple myeloma [2].

Osteoclasts, which play a critical role in pathological bone loss, are multinucleated giant cells (MNCs) originating from hematopoietic mononuclear precursors of the monocyte/macrophage lineages [3]. Osteoclast differentiation (or osteoclastogenesis) is an intricate process that involves many stages, such as differentiation to tartrate-resistant acid phosphatase (TRAP)-positive cells, fusion to form multinucleated cells, activation to resorb bone, and spontaneous apoptosis [4].

During the differentiation of monocyte/macrophage lineage precursor cells into multinucleated osteoclasts, receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony stimulating factor (*M*-CSF) are two essential cytokines recognized as potent inducers of osteoclastogenesis [5,6]. RANKL, also termed tumor necrosis factor-related activation-induced cytokine (TRANCE), osteoclast differentiation factor (ODF), is identified as a protein belonging to the tumor necrosis factor (TNF) superfamily. The interaction of RANKL with members of the TNF receptor (TNFR) superfamily, osteoprotegerin (OPG) and receptor activator of nuclear factor-κB (RANK), is a prerequisite step to induce the initiation of osteoclast differentiation [3]. A previous study revealed that RANKL genetic deletion in mice causes not only osteoclast dysfunction in vitro, but also osteopetrotic conditions and defective dental erosion in vivo [7]. *M*-CSF, also called colony-stimulating factor-1 (CSF-1), plays a critical role in the survival and proliferation of early osteoclast precursors. The binding of *M*-CSF to its cell surface receptor, colony-stimulating factor-1 receptor (*c*-fms), generates the activation of intracellular mediators, including extracellular signal regulated protein kinases (ERK) 1/2 and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling, triggering osteoclast differentiation [8]. It has been previously shown that op/op mice with a point mutation of CSF-1 gene cannot express functional *M*-CSF, suffering from osteoclast-poor osteopetrosis. In addition, this abnormal condition is rescued by treatment with a soluble form of *M*-CSF [9]. As illustrated in Fig. 1, the *M*-CSF receptor transmits survival signals to osteoclasts, and RANKL mediates osteoclastogenesis through binding to its receptor RANK on osteoclast precursors [10]. The Binding of RANKL to its receptor, RANK leads to recruitment of TNF receptor-associated factor 6 (TRAF6) to the cytoplasmic domain of RANK leading to activation of TRAF6. TRAF6 activation in turn triggers various downstream signaling pathways such as the nuclear factor-κB (NF-κB), three mitogen activated protein kinases (MAPKs) including p38 MAPK, ERK and *c*-jun-*N*-terminal kinase (JNK) [11], as well as activation of activator protein-1 (AP-1), Src/PI3K/Akt axis, the calcium signaling cascade and so on [2,12]. These signaling pathways ultimately lead to induction and

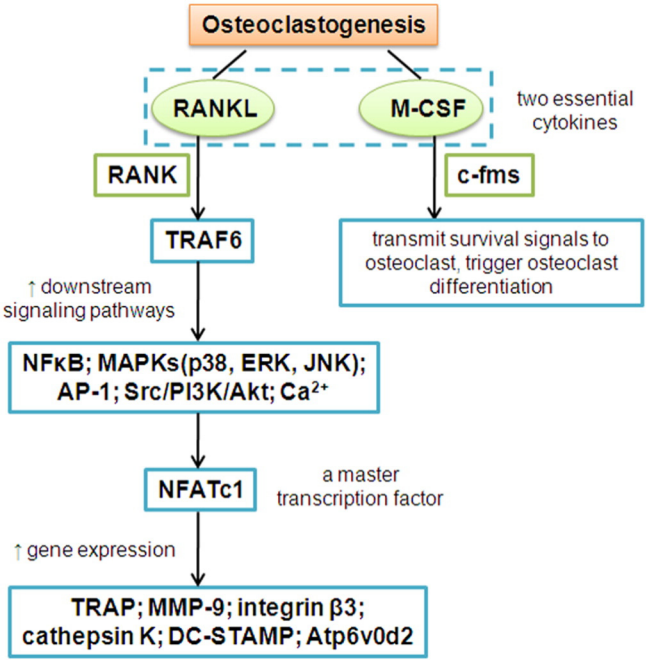

Fig. 1. The RANKL-RANK signaling involved in osteoclastogenesis.