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Review

Roles of non-canonical Wnt signaling pathways in bone resorption

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ABSTRACT

Background: Wnt is a cytokine involved in the development and homeostasis of various organs. In 2001, low-density lipoprotein receptor-related protein 5 (LRP5) was identified as the gene responsible for osteoporosis pseudoglioma syndrome and regulation of bone mass. Since LRP5 belongs to the low-density lipoprotein receptor family, this finding garnered the attention of researchers in the bone, mineral, and Wnt research fields. The role of Wnt in bone formation and resorption has since been extensively studied. Wnt/β-catenin signals are known to play a role in bone resorption. The activation of these signals in osteoblast lineage cells such as osteoblasts and osteocytes induces the expression of osteoprotegerin and then inhibits osteoclast formation.

Highlight: Wnt5a binds to Ror2 receptors and activates non-canonical signaling pathways, thereby promoting osteoclast differentiation and bone-resorbing activity. In contrast, Wnt16 activates non-canonical Wnt signaling in osteoclast precursor cells and suppresses the Rankl-induced activation of Nf-κb and Nfatc1, thereby inhibiting osteoclast differentiation.

Conclusion: Wnt5a and Wnt16 tightly regulate osteoclast differentiation and function in order to maintain bone mass under physiological conditions.

Contents

1. Introduction

In bone tissue, bone resorption and formation continue throughout the life cycle. This process is called bone remodeling and is necessary for maintaining bone mass and calcium concentrations in bodily fluids. Disruptions in the balance between bone resorption and formation lead to the development of osteopenia or osteopetrosis.

Osteoclasts, multinucleated cells responsible for bone resorption, differentiate from monocyte-macrophage-lineage cells [1]. The differentiation of osteoclasts is tightly regulated by osteoblast linage cells such as osteoblasts [2] and osteocytes [3,4]. Osteoblasts and osteocytes produce receptor activator of Nf-κb ligand (Rankl), a cytokine essential for osteoclast differentiation. In addition, osteoblasts produce macrophage colony-stimulating factor (M-csf),

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another cytokine necessary for osteoclast differentiation. Rankl expression is induced by bone-resorbing factors such as 1α,25-dihydroxy vitamin D_3, interleukin 6, and parathyroid hormone (Pth) [1]. When Rankl binds to its receptor Rank, the nuclear factor-κb (Nf-κb) pathway and c-Fos are activated. The expression of nuclear factor-activated T cell cytoplasmic 1 (Nfatc1), a master transcription factor of osteoclast differentiation, is subsequently induced, and osteoclast precursor cells then differentiate into osteoclasts [5,6]. Osteoblasts and osteocytes also produce osteoprotegerin (Opg), which is the decoy receptor of Rankl. Opg inhibits osteoclast differentiation by interfering with the interaction between Rankl and Rank [7]. In this review, we discuss recent findings on the roles of non-canonical Wnt signaling pathways in osteoclast differentiation and function.

2. Wnt signaling

Wnt ligands activate β-catenin-dependent canonical and -independent non-canonical signaling pathways [8] (Fig. 1). Wnt/β-catenin signaling pathways: In the absence of the Wnt ligand, β-catenin is phosphorylated by a degradation complex composed of Axin, Apc, GSK-3β, and CK1. Phosphorylated β-catenin is degraded by the ubiquitin-proteasome pathway. Therefore, intracellular β-catenin is maintained at a low level. When the Wnt ligand binds to a receptor complex composed of Frizzled receptor and Lrp5 or Lrp6, β-catenin accumulates in the cytoplasm due to suppressed activity of the degradation complex. Accumulated β-catenin translocates to the nucleus and induces the expression of the target gene together with T-cell factor and lymphoid enhancer factor.

Among β-catenin-independent signaling pathways, Wnt5a, a typical non-canonical Wnt ligand, activates β-catenin-independent signaling pathways. Receptor tyrosine kinase-like orphan receptors (Rors) 1/2 function as co-receptors of Wnt5a [9]. Transcription factors involved in non-canonical Wnt signaling have not yet been identified. Therefore, studies on these signaling pathways have been more challenging than those on the Wnt/β-catenin signaling pathways. In the Wnt/Ca^{2+} pathways, intracellular calcium increases and calmodulin-dependent protein kinase II and protein kinase C are activated. Wnt/planar cell polarity pathways: small G proteins such as Rac and Rho are activated, and these pathways are involved in cell motility and cilia orientation.

3. Roles of Wnt5a in osteoclast differentiation

The importance of the Wnt/β-catenin signaling pathways in osteoclast differentiation was first reported using mouse genetic approaches [10]. Mice whose osteoblasts expressed constitutively active forms (CA) of β-catenin (CA-Ob-β-catenin mice) exhibited a high bone mass with impaired osteoclast formation. Opg expression increased in bone tissues from CA-Ob-β-catenin mice. Thus, the activation of the Wnt/β-catenin signaling pathways in mature osteoblasts induces the expression of Opg, which in turn suppresses bone resorption.

The Wnt/β-catenin signaling pathways play important roles in bone resorption. However, the involvement of the non-canonical Wnt signaling pathways in bone resorption currently remains unclear. We demonstrated that Wnt5a secreted from osteoblasts binds to Ror2 receptors and promotes the expression of Rank through activation of c-Jun N-terminal kinases, thereby enhancing Rankl-induced osteoclastogenesis (Fig. 2) [11]. We initially examined the expression of Wnt ligands in osteoblasts and bone-marrow macrophages as osteoclast precursors. Among the 19 Wnt ligands, Wnt5a was strongly expressed in osteoblasts, but not in bone marrow macrophages. Osteoblasts and bone marrow macrophages express Frizzled and Ror2, but not Ror1, suggesting that Wnt5a is involved in bone formation and resorption. We investigated whether Wnt5a influenced osteoclast formation *in vitro*. Wnt5a enhanced Rankl-induced osteoclast formation in bone marrow macrophage cultures from wild-type mice, but not in

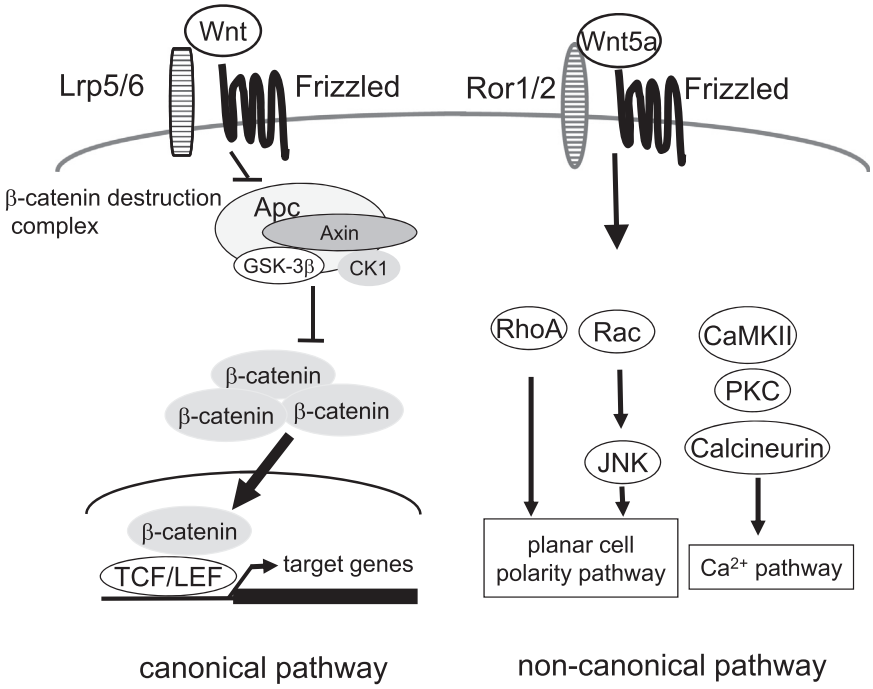

Fig. 1. The Wnt signaling pathways. Binding of Wnt ligands with the receptor complex of frizzled and Lrp5/6 inactivates the β-catenin destruction complex, which in turn induces the cytosolic accumulation and nuclear translocation of β-catenin. Nuclear β-catenin with Tcf1 induces the transcription of target genes. The receptor complex of frizzled and Ror1/2 activates planar cell polarity pathways through small GTPases such as Rho and Rac and also activates Ca^{2+}-sensitive enzymes such as Ca^{2+}-calmodulin-dependent protein kinase II and protein kinase C.

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