Mini Review

The non-canonical Wnt5a/Ror2 signaling pathway in bone metabolism

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Wingless-type MMTV integration site (Wnt) family molecules, a family of secreted glycoproteins have now gathered attention as a therapeutic target. Drug innovation targeting the canonical Wnt pathway is in the most interest since its molecular mechanism is well understood and clinical trials are in progress for osteoporosis. Recent findings have revealed the contribution of the non-canonical Wnt pathway in malignant tumors suggesting this pathway as a new treatment target, but it is relatively less understood. Recently, several reports have demonstrated the involvement of the non-canonical Wnt pathway in the bone metabolism. Therefore, we have compiled the current understanding of the non-canonical Wnt pathway in association with bone metabolism.

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Introduction

Wingless-type MMTV integration site (Wnt) family molecules, a family of secreted glycoproteins, control multiple developmental processes during embryogenesis and also are involved in tissue maintenance and remodeling by mediating stem cell proliferation or fate after birth[1]. The Wnt signaling pathway is also involved in the pathophysiology of skeletal diseases such as osteoporosis-pseudoglioma syndrome (OPPG), sclerosteosis and Robinow syndrome. Moreover, participation of Wnt molecules in malignancies has also been reported[2-8]. Therefore, drug innovation targeting this pathway is gathering attention. We reviewed the current understanding of the non-canonical Wnt signaling pathway, focusing on the role of Wnt5a/ receptor tyrosine kinase-like orphan receptor (Ror)2, in bone metabolism.

The Wnt signaling pathway

Wnt molecules are known to activate intracellular signaling through either β-catenin-dependent (canonical) or β-catenin-independent (non-canonical) pathways. The Wnt molecules that activate the canonical pathway first bind to their receptors frizzled (Fzd) and low-density lipoprotein receptor-related protein (LRP) and inactivate glycogen synthase kinase (GSK)-3β resulting in enhanced expression

Table 1 Expression of Frizzled (Fzd), LRP and Ror on osteoblasts and osteoclasts

	Fzd1	Fzd2	Fzd3	Fzd4	Fzd5	Fzd6	Fzd7	Fzd8	Fzd9	LRP5	LRP6	Ror1	Ror2
Osteoblast													
Human	+	+	+	+	+ or -	+	+	+	+	+	+	+	+
Mouse	+	+	+	+	+	+	+	-	-	+	+	-	+
Osteoclast													
Human	+	+	+	+	+	+	+	+	+	+or-	+	N/D	N/D
Mouse	+	+	+	+	+	+	+	-	-	+or-	+	-	+

and nuclear translocation of β-catenin, which regulates the expression of target genes[9]. On the other hand, Wnt5a, one of the most common Wnt molecules that activate the non-canonical pathway binds to Fzd and its co-receptor, Ror2. There are at least three different signaling pathways that are involved in the non-canonical pathway; Wnt5a/Ca^{2+}, Wnt5a/Rho and Wnt5a/JNK pathways[10, 11]. After the ligand binds to Fzd-Ror2 complex, dishevelled (DVl) and phospholipase C (PLC) is activated. PLC induces accumulation of intracellular cytoplasmic Ca^{2+} and further activation of protein kinase C (PKC), Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and nuclear factor of activated T cells (NFAT) that inhibits the β-catenin pathway; the Wnt/Ca^{2+} pathway. On the other hand, DVl activation triggers its downstream Rho and Rac activation, where Rho activate the downstream kinase Rho-associated kinase (ROCK); the Wnt5a/Rho pathway, and Rac activate c-jun N-terminal kinase (JNK); the Wnt5a/JNK pathway[12]. Expression of Wnt receptors was summarized in Table 1[13-19].

Role of Wnt molecules in skeletal formation in relation to diseases

The structure of Wnt molecules are highly conserved in drosophila, zebrafish, xenopus, mice and humans[20]. As shown in Table 1, expression pattern of the receptors in osteoblasts and osteoclasts are also common in mice and humans. Thus, the roles of the Wnt signaling pathway in the skeletal system have been investigated intensively in both human and animals. OPPG, a rare human disease characterized by low bone mass and developing fractures and deformation, was first reported to be caused by loss-of-function mutation of LRP5, a co-receptor of Fzd activating the canonical Wnt signaling pathway[2]. Several reports support that impaired canonical Wnt signaling pathways cause loss of bone mass and that its gain of function results in bone formation[21-23].

Regarding non-canonical pathway, Yamaguchi et.al. reported Wnt5a-deficient mice with multiple organ dysplasia such as dwarfism, craniofacial abnormality, and short limbs and tails[24]. Similar phenotypes can be observed in Ror2 knockout mice[25] and in patients with Robinow syndrome, a disease caused by loss of Ror2 activity[6]. These reports clearly show the importance of non-canonical Wnt signaling pathway in skeletal diseases and also imply the different roles of canonical and non-canonical signaling pathway on the skeletal system. In addition to skeletal diseases, the non-canonical pathway is involved in carcinomas in the lung, breast, prostate and also malignant melanoma[7] and gastric cancer[8]. Thus, the non-canonical pathway is also a target for anti-tumor therapy. However, most recent reports highlight the importance of the Wnt5a/Ror2 signaling pathway in osteoblasts and osteoclasts[14, 18] as key players in the bone metabolism.

Non-canonical Wnt signaling pathway in osteoblasts

Osteoblasts are the key players for bone formations that differentiate from mesenchymal stem cells (MSCs). Among the non-canonical Wnt signaling pathways, Wnt5a is the most investigated. $Wnt5a^{+/-}$ mouse shows reduced numbers of proliferating cells in both the progress zone and the primitive streak mesoderm[24]. This can be explained by the altered proliferation of mesenchymal progenitor cells by inhibition of Wnt5a signaling pathway. A report by Guo et al. described the suppressed proliferation of calvarial cells derived from $Wnt5a^{+/-}$ mice[26]. They have also de-

scribed the impaired osteoblastic gene expression of runt-related transcription factor 2 (RUNX2), osterix and alkaline phosphatase (ALP). In addition, Takada et al. demonstrated that Wnt5a promotes osteoblast differentiation through repressing peroxisome proliferator-activated receptor γ (PPAR γ), the master regulator of adipogenesis[27]. Thus, Wnt5a is considered to be involved in regulating the cell fate of MSCs that possess multipotency and control bone metabolism[28].

A recent report revealed that calvarial cells of Wnt5a$^{+/-}$ mice showed impaired osteoblast differentiation. However, that of Ror2$^{+/-}$ mice showed preserved osteoblast differentiation. Furthermore, inhibition of Ror2 resulted in higher bone mass and less progression of bone destruction in collagen induced arthritis mice[18]. This suggests the discontinuous procedure of Wnt5a and Ror2 in murine osteoblasts. On the other hand, we have reported that over expression of Wnt5a in human MSCs induces up-regulation of RUNX2 the master regulator of osteoblast differentiation[14], and over-expression of Ror2 with enhanced mineralization. Moreover, inhibition of Wnt5a or Ror2 resulted in complete inhibition of osteoblast differentiation of human MSCs. These data demonstrate that the Wnt5a/Ror2 signaling pathway positively regulates osteoblast differentiation in human. Our findings are supported by human system reported by Afzal et al.; the loss of Ror2 activity induced recessive form of Robinow syndrome[6]. Therefore, the non-canonical Wnt5a/Ror2 signaling pathway plays an important role in differentiation of mesenchymal progenitor cells.

Non-canonical Wnt5a/Ror2 signaling pathway in osteoclasts

The Wnt5a/Ror2 signaling pathway in association with osteoclasts is less understood. Santiago and coworkers recently demonstrated that non-canonical Wnt5a and Wnt5b tend to induce osteoclast differentiation in both mice and humans[29]. Analysis of Wnt5a or Ror2 knockout mice revealed the dynamic details of the Wnt5a/Ror2 signaling pathway *in vivo* and *in vitro*[18]. Maeda et.al. demonstrated that Wnt5a in osteoblasts promotes osteoclast differentiation through the up-regulation of receptor activator of nuclear factor-κB (RANK) expression on osteoclast precursors. Moreover, increased bone mass was observed in Ror2-deficient mice and soluble Ror2, an inhibitor of Wnt5a/Ror2 signaling pathway, suppressed bone destruction of collagen induced arthritis model. This report has shown that the Wnt5a/Ror2 signaling pathway induces bone resorption without affecting osteoblast differentiation and bone formation in mice. Thus, these reports indicated that Wnt5a/Ror2 pathway is a suitable target for inhibition of bone formation. On the other hand, Wnt5a/Ror2 signaling pathway is also reported to inhibit RANKL-RANK signaling pathway of osteoclasts through inhibition of NFATc1[30]. Moreover, as stated earlier, several investigations have suggested that inhibition of Wnt5a/Ror2 signaling pathway will impair the differentiation of human osteoblasts. Thus, further investigation is necessary before clinical use of its inhibitor is considered.

New treatment strategy; targeting the Wnt signaling pathway

Classically, LiCl, widely used on mania, is known as an inhibitor of GSK-3β[31] which could lead to up-regulation of the canonical Wnt signaling pathway. Multiple compounds targeting the canonical pathway are currently under investigation. For instance, sclerostin, DKK-1 (inhibitors of canonical pathway) and soluble Frizzled-related protein (sFRP) (inhibitor of canonical and non-canonical pathway) are known as inhibitors of the Wnt signaling pathway and clinical trials are under way for treatment of osteoporosis[9, 32]. As reviewed above, both canonical and non-canonical Wnt signaling pathway are candidates as a novel treatment strategy for skeletal diseases. sFRP inhibits non-canonical Wnt signaling pathway as well as canonical Wnt signaling pathway by binding Frizzled. However, due to the limited knowledge of its role in the bone metabolism, targeting the non-canonical Wnt signaling pathway has lagged behind.

Inflammation is considered as a regulator of the non-canonical Wnt signaling pathway. Among cytokines, IL-6/STAT3 pathway have been reported to up-regulate Wnt5a gene expression[33]. And more recently, we have reported that IL-1β promotes osteoblast differentiation of human MSCs through up-regulating Wnt5a/Ror2 signaling pathway[14] (Fig.1). Promoted osteoblast differentiation was completely inhibited by siRNA of Wnt5a or Ror2. Since our experiments were performed with hMSCs single culture, autocrine Wnt5a/Ror2 signaling pathway is considered to be essential for bone formation in human. MSCs produce osteoprotegerin and inhibit osteoclast differentiation[34]. However, differentiated osteoblasts induce osteoclast differentiation through RANK-RANKL pathway. Thus we also evaluated the inflammatory cytokine-treated osteoblasts and

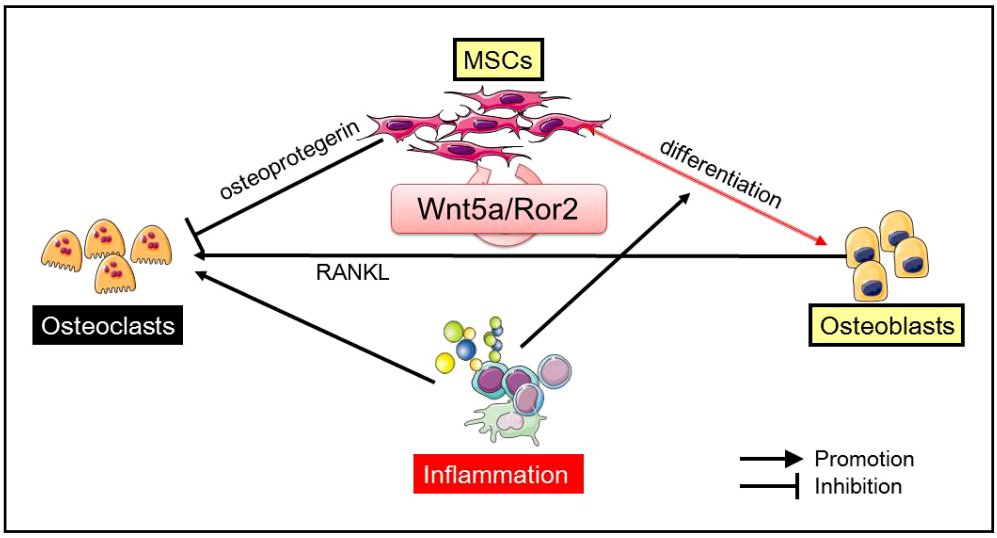

Fig.1 MSCs maintain homeostasis against inflammation

Both inflammation and osteoblasts act to promote osteoresorption by osteoclasts. However, our reports have proved the ability of MSCs to inhibit osteoclastogenesis and to differentiate into osteoblasts even under inflammatory stimuli. These show the mechanism of homeostasis-maintenance by MSCs. IL-1β induced osteoblasts also produce osteoprotegerin, thus they don't induce bone resorption.

elucidated that osteoprotegerin was highly induced and did not induce osteoclast differentiation in co-culture systems. Given these findings and with the perspective of bone repair in rheumatoid arthritis (RA) patients, we have considered that intra-articular transplantation of human MSCs would be a useful and novel treatment tool and further investigation is ongoing.

Future developments of Wnt5a/Ror2 signaling pathway and bone metabolism

The Wnt5a/Ror2 signaling pathway is also known to alter the behavior of malignant cells[7, 8]. Recent works gave clarified the critical role of Wnt5a/Ror2 in epithelial mesenchymal transition (EMT)[35], which act in invasion or metastasis of malignant tumors[36]. EMT is also involved in tissue repair by producing extracellular matrix which occurs under tissue damage (i.e. inflammation). This implies the applicability of epithelial cells for regeneration of mesenchymal tissue.

Although the Wnt signaling pathway is a suitable target aimed at bone regeneration, the direct association of Wnt molecules with osteocyte differentiation is unknown. Therefore, development of drugs targeting this pathway should be carried out with care and clarifying its exact role in osteocyte differentiation is essential for establishment of MSCs therapy on bone regeneration.

Conclusion

The role of the Wnt5a/Ror2 signaling pathway is still uncertain. Although Wnt molecules are highly conserved among different species, there seems to be different roles among different species. A recent investigation uncovered the indirect effect of Wnt5a on induction of inflammation[37], which will lead Wnt5a-targeted drug innovation. Effects on skeletal system should be monitored with the greatest possible care.

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