

## COMMENTARIES

### A New PPAR- $\gamma$ Function in Bone

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**Commentary on:** Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. *Nat Med.* 2007 Dec;13(12):1496-503.

**Thiazolidinediones (TZDs) are antidiabetic drugs that improve insulin sensitivity through activation of PPAR- $\gamma$  (peroxisome proliferator activated receptor- $\gamma$ ). Recent clinical studies have suggested a negative regulatory effect of TZDs on bone mineral density (BMD). However, the mechanisms of TZD action in bone have not been fully elucidated. By generating osteoclast-specific PPAR- $\gamma$  knockout mice, Wan and coauthors clearly show the significance of PPAR- $\gamma$  function in osteoclastogenesis (1). Their work identifies PPAR- $\gamma$  as a potential therapeutic target for the treatment of osteoporosis.**

#### Control of Bone Metabolism by PPAR- $\gamma$

Bone formation by osteoblasts and bone resorption by osteoclasts are essential in controlling the amount of bone tissue. Osteoblasts are differentiated from mesenchymal stem cells that can also differentiate into myoblasts, chondrocytes and adipocytes. Control of transdifferentiation switching between adipocytes and osteoblasts is a critical problem for metabolic diseases, aging and osteoporosis. In recent studies, many osteoblast and adipocyte differentiation regulators have been identified. In particular, PPAR- $\gamma$  is known as a positive adipocyte differentiation regulator. PPAR- $\gamma$  is a member of the nuclear receptor superfamily and regulates mRNA expression levels of target genes in a ligand-dependent manner. Many PPAR- $\gamma$  ligands including fatty acid derivatives and synthetic compounds have

been identified, among which TZDs became the most popular PPAR- $\gamma$  ligands used as antidiabetic drugs.

However, recent clinical studies have shown that type 2 diabetes patients treated with TZDs exhibit decreases in bone formation and bone mass (2). These effects suggest that PPAR- $\gamma$  may regulate bone remodeling. One possible mechanism has been suggested from previous studies using heterozygous PPAR- $\gamma$ -deficient mice (3); these animals exhibit increases in bone mass and bone formation. Other groups have reported that PPAR- $\gamma$  ligands inhibit osteoblast differentiation in bone marrow-derived mesenchymal stem cells (4). These data indicate that in bone PPAR- $\gamma$  inhibits osteoblastogenesis.

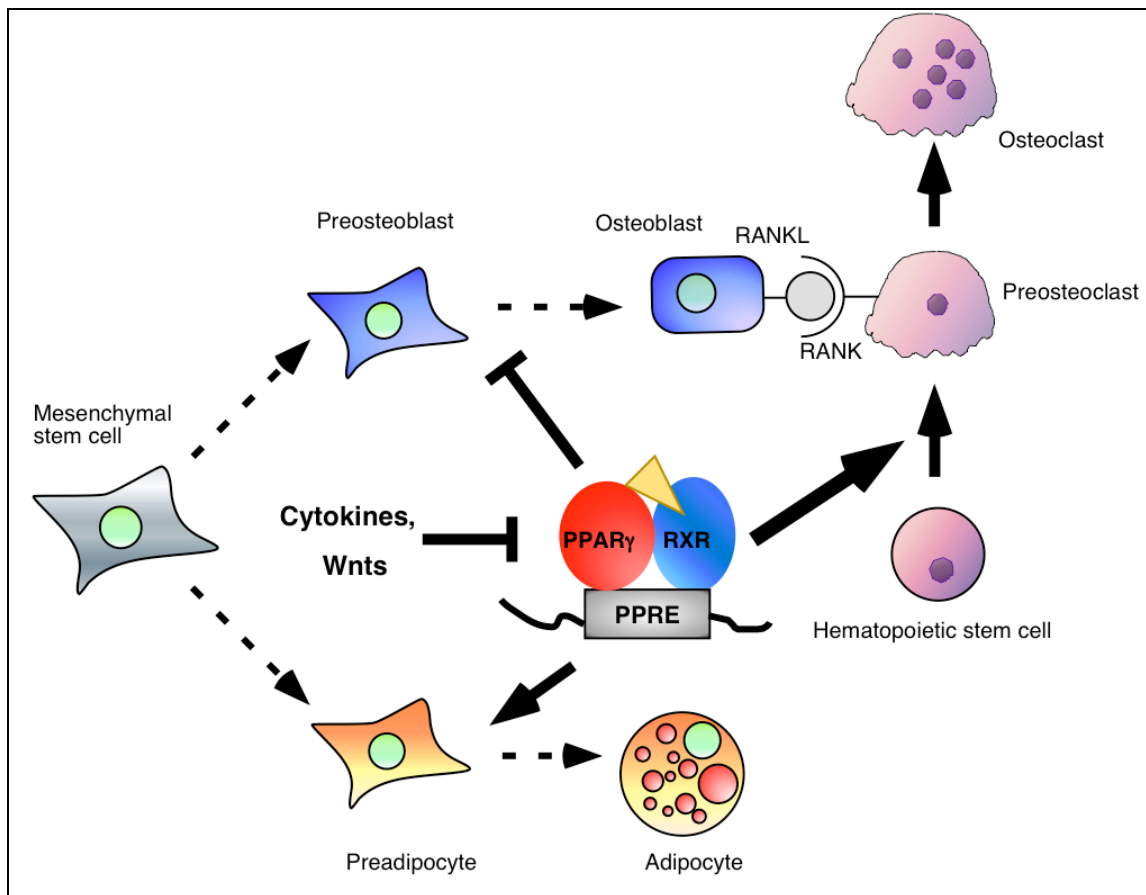
#### Extracellular Signaling Regulates PPAR- $\gamma$ Function in Mesenchymal Stem Cells

Moreover, recent studies have shown that several signaling pathways that affect osteoblast differentiation can also regulate PPAR- $\gamma$  function. Previously, we described two signaling pathways that switch the cell fate decision from adipocytes to osteoblasts. The first signaling pathway is a TAK1/TAB1/NF- $\kappa$ B-inducing kinase (NIK) cascade activated by TNF- $\alpha$  and IL-1, and the activated NF- $\kappa$ B blocks DNA binding by PPAR- $\gamma$ , attenuating PPAR- $\gamma$ -mediated adipogenesis (5). The second pathway is the noncanonical Wnt pathway through CaMKII-TAK1/TAB2-NLK. Activated by a noncanonical Wnt ligand (Wnt-5a), NLK transrepresses PPAR- $\gamma$  transactivation

through a histone methyltransferase, SETDB1. Wnt-5a induces phosphorylation of NLK, leading to formation of a corepressor complex that downregulates PPAR- $\gamma$  target genes through histone H3-K9 methylation (6). Thus, during mesenchymal stem cell differentiation, two signaling pathways lead to an osteoblastic cell lineage decision through two distinct modes of PPAR- $\gamma$  transrepression.

### PPAR- $\gamma$ Promotes Osteoclastogenesis

Although PPAR- $\gamma$  is expressed in osteoclast precursor cells, its role in the regulation of osteoclastogenesis has been unclear. Wan and colleagues now illustrate a new function for PPAR- $\gamma$  in osteoclastogenesis (1) (Fig. 1).



**Fig. 1.** PPAR- $\gamma$  function in osteoclastogenesis and osteoblastogenesis. PPAR- $\gamma$  inhibits osteoblastogenesis and promotes osteoclastogenesis. Cytokines such as IL-1, TNF- $\alpha$  and Wnt signals (Wnt-5a, Wnt-10b) suppress the transactivation function of PPAR- $\gamma$ .

In this work, mice with a deletion of PPAR- $\gamma$  in osteoclasts, but not in osteoblasts, developed a phenotype of increased bone mass and density and extramedullary hematopoiesis. The authors also used the converse approach to activate PPAR- $\gamma$  with rosiglitazone in wildtype mice. This treatment accelerated osteoclast differentiation and bone resorption in a

PPAR- $\gamma$ -dependent manner (1). Moreover, in this study *c-fos*, which was known as a key regulator of the macrophage/osteoclast lineage and bone remodeling (7), was identified as a PPAR- $\gamma$  direct target gene. Interestingly, Wan *et al.* also examined the effects of PPAR- $\gamma$  antagonists (GW9662 and T0070907) in osteoclasts and found that

these two compounds reduced c-fos mRNA expression in a PPAR- $\gamma$ -dependent manner.

### What Is the Role of PPAR- $\gamma$ in Late Osteoclastogenesis?

Nevertheless, this elegant and sophisticated study leaves several points unanswered. First, *Tie2* promoter-driven Cre expression was used for osteoclast-specific knockout of the PPAR- $\gamma$  gene. This promoter is activated in endothelial cells that are precursors of several cell types besides osteoclasts (8), so the differentiation of other cells might also be affected. Therefore, the function of PPAR- $\gamma$  at late stages of osteoclastogenesis remains unclear. Consequently, it is necessary to analyze PPAR- $\gamma$  function in osteoclasts by using other promoter-driven Cre mice such as *cathepsin K* Cre mice (9); *cathepsin K* is a late stage osteoclast marker gene.

It also remains unclear whether PPAR- $\gamma$ -dependent promotion of osteoclastogenesis is more significant than PPAR- $\gamma$ -dependent inhibition of osteoblastogenesis. To address this question, generation of osteoblast- or mesenchymal stem cell-specific PPAR- $\gamma$  KO mice will be necessary to fully understand the role of PPAR- $\gamma$  in the regulation of bone remodeling.

### What Are the Coregulators of PPAR- $\gamma$ in Osteoclasts?

Another issue is that PPAR- $\gamma$  appears to regulate different sets of genes in hematopoietic cells and mesenchymal cells, as PPAR- $\gamma$  ligands cannot induce adipocyte differentiation from committed preosteoclasts. This difference may be due to differences in transcriptional factors present or in chromatin structure. Recent studies have revealed the importance of epigenetic histone modifications (acetylation, methylation, phosphorylation, and ubiquitination) at PPAR- $\gamma$  binding sites for adipocyte/osteoblast differentiation.

### Can SPPARMs Be Used as Drugs for Osteoporosis?

In conclusion, Wan and colleagues have provided the first evidence for PPAR- $\gamma$  function in osteoclasts (Fig. 1). Currently, a number of synthetic compounds that influence the activity of nuclear receptors like SERMs (selective estrogen modulators such as tamoxifen and raloxifen) are used for the prevention of osteoporosis. The new study suggests that some PPAR- $\gamma$  antagonists or selective PPAR- $\gamma$  modulators (SPPARMs) may be used for the treatment of osteoporosis, though their possible adverse effects in patients with type 2 diabetes must be fully examined. The key issue would be whether a compound could be developed that antagonizes PPAR- $\gamma$  in mesenchymal osteoblast progenitors and hematopoietic osteoclast precursors in the bone marrow but is agonistic in visceral and subcutaneous adipose progenitors.

**Conflict of Interest:** None reported.

**Peer Review:** This article has been reviewed by Toshio Matsumoto.

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