

# 15-Deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> as a potential regulator of bone metabolism via PPAR $\gamma$ -dependent and independent pathways: a review

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**Abstract:** Bone metabolism is a complex physiological process that primarily involves osteoblast-mediated bone formation and osteoclast-mediated bone resorption, both of which are regulated by a variety of biological factors. There is increasing evidence that peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is a member of the nuclear receptor superfamily and plays an important role in lipid metabolism and bone metabolism. Through the PPAR $\gamma$ -dependent pathway, 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> (15d-PGJ<sub>2</sub>) promotes the formation of marrow adipocytes and inhibits the formation of osteoblasts, resulting in bone loss and increasing the risk of fracture and osteoporosis. Recent studies have found that through the PPAR $\gamma$ -independent pathway, 15d-PGJ<sub>2</sub> plays a regulatory role in bone metastasis of breast cancer, which can inhibit osteoclastogenesis and reduce bone destruction. The purpose of our review is to summarize the recent progress in elucidating the mechanisms and effects of 15d-PGJ<sub>2</sub> in bone metabolism, which can serve as a novel therapeutic target for bone tumors, osteoporosis, rheumatoid arthritis (RA), and other bone diseases.

**Keywords:** bone metabolism, osteoblast, adipogenesis, osteoporosis, rheumatoid arthritis, bone metastasis

## Introduction

Bone is a dynamically changing tissue that constantly adapts to vertebrate life to maintain bone shape, size, and structural integrity, and bone regulates mineral homeostasis in the body.<sup>1</sup> Bone formation and bone resorption are mediated by osteoblasts and osteoclasts, respectively, which are the two main processes of bone metabolism.<sup>2</sup> Formation and resorption are tightly coupled under physiological conditions to maintain bone mass. In the pathological process of osteoporosis, bone resorption exceeds bone formation and can cause an imbalance in bone metabolism and a net loss of bone.<sup>3</sup> The bone marrow stroma includes mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), which can differentiate into a variety of cell types common to bone.<sup>4</sup> Two main types of cells in bone have different developmental origins: osteoblasts are derived from mesenchymal lineage,<sup>5</sup> and osteoclasts are derived from hematopoietic lineage.<sup>6</sup> Many biological factors regulate osteoblast differentiation and osteoclast differentiation, thus affecting bone formation and bone resorption and playing a role in bone metabolism.

Prostaglandins (PGs) are a class of bioactive compounds produced by arachidonic acid (AA) that have a variety of regulatory functions in the human body.<sup>7</sup> Different types of PGs have complex functions in different target cells.<sup>8</sup> 15d-PGJ<sub>2</sub> is an

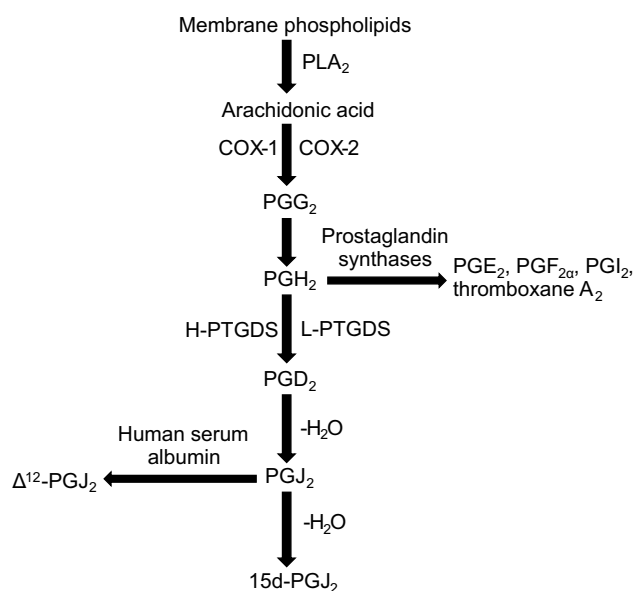
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endogenous ligand for PPAR $\gamma$ , which is produced by the cyclooxygenase (COX)-mediated AA metabolism pathway.<sup>8-10</sup> Studies have shown that ligand-activated PPAR $\gamma$  alters the fate of bone marrow MSCs by promoting the differentiation of adipocytes and inhibiting the differentiation of osteoblasts.<sup>11-13</sup> Numerous studies have confirmed that 15d-PGJ<sub>2</sub> promotes the differentiation of adipocytes and inhibits the differentiation of osteoblasts by activating PPAR $\gamma$ , thereby inhibiting bone formation and causing bone loss.<sup>9,10</sup> Recently, studies have shown that through a PPAR $\gamma$ -independent pathway, 15d-PGJ<sub>2</sub> inhibits bone destruction caused by bone metastasis in breast cancer by suppressing osteoclast differentiation and bone resorption.<sup>14</sup> Treatment with 15d-PGJ<sub>2</sub> also inhibits bone loss caused by estrogen deficiency.<sup>14</sup> 15d-PGJ<sub>2</sub> may be a potential regulator of bone metabolism, and drugs targeting 15d-PGJ<sub>2</sub> may offer new prospects for metabolic bone diseases. To further explore these prospects, this review was performed.

## The biosynthesis and bioactivity of 15d-PGJ<sub>2</sub>

The biosynthesis of 15d-PGJ<sub>2</sub> is based on the continuous action of several enzymes, the general pathway of which is illustrated in Figure 1.<sup>15</sup> Under the action of enzyme phospholipase A<sub>2</sub> (PLA<sub>2</sub>), AA is released by membrane phospholipids as the first step of this metabolic pathway.<sup>8,15</sup> Under the action of COX-1 or COX-2, AA first produces PGG<sub>2</sub> and then PGH<sub>2</sub>.<sup>8,16</sup> PGH<sub>2</sub> is an unstable intermediate that can be converted into a series of stable prostaglandins by their specific prostaglandin synthases, including PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2 $\alpha$</sub> , PGI<sub>2</sub>, and thromboxane A<sub>2</sub>.<sup>16,17</sup> PGD<sub>2</sub> is synthesized under the action of prostaglandin D synthase (PTGDS, including H-PTGDS and L-PTGDS).<sup>18,19</sup> Subsequently, PGD<sub>2</sub> readily undergoes chemical dehydration, which in turn forms the cyclopentenone prostaglandin PGJ<sub>2</sub>.<sup>9,20</sup> Both 15d-PGJ<sub>2</sub> and  $\Delta^{12}$ -PGJ<sub>2</sub> are produced by PGJ<sub>2</sub>, but the latter requires the participation of albumin.<sup>21</sup>

Unlike other types of PGs, 15d-PGJ<sub>2</sub> contains a cyclopentenone ring structure.<sup>8</sup> The cyclopentenone ring has an electrophilic  $\alpha$ ,  $\beta$ -unsaturated ketone moiety that provides a unique bioactivity spectrum for 15d-PGJ<sub>2</sub>.<sup>22</sup> In 1995, Forman and Tontonoz<sup>9</sup> examined the ability of AA metabolites to act as ligands to activate PPAR $\gamma$  and identified 15d-PGJ<sub>2</sub> as its natural ligand. Although 15d-PGJ<sub>2</sub> has a lower affinity for PPAR $\gamma$  than steroid hormones for its homologous intracellular receptors, it is the highest



**Figure 1** Biosynthesis of 15d-PGJ<sub>2</sub>. In the first step, membrane phospholipids are catalyzed by the action of the PLA<sub>2</sub> enzyme to release AA. In the second step, AA is sequentially metabolized to PGG<sub>2</sub> and then to PGH<sub>2</sub> by COX-1 or COX-2. Subsequently, PGE<sub>2</sub>, PGF<sub>2 $\alpha$</sub> , PGI<sub>2</sub>, and thromboxane A<sub>2</sub> were converted from PGH<sub>2</sub> by their respective prostaglandin synthetase. The rate-limiting enzyme used to synthesize PGD<sub>2</sub> is PTGDS, both H-PTGDS and L-PTGDS. PGD<sub>2</sub> readily undergoes chemical dehydration, losing water to form the cyclopentenone prostaglandin PGJ<sub>2</sub>. In the final step, 15d-PGJ<sub>2</sub> and  $\Delta^{12}$ -PGJ<sub>2</sub> are produced from PGJ<sub>2</sub> by albumin-independent and albumin-dependent reactions, respectively.

**Abbreviations:** 15d-PGJ<sub>2</sub>, 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub>; PLA<sub>2</sub>, phospholipase A<sub>2</sub>; AA, arachidonic acid; PG, prostaglandin; COX, cyclooxygenase; PTGDS, prostaglandin D synthase.

affinity natural ligand of PPAR $\gamma$  identified to date.<sup>8</sup> Due to its specific cyclopentenone ring structure and ligand activity that activates PPAR $\gamma$ , 15d-PGJ<sub>2</sub> plays a regulatory role in many physiological and disease processes. Studies have shown that 15d-PGJ<sub>2</sub> promotes apoptosis<sup>23,24</sup> and exerts anti-inflammatory,<sup>16</sup> anti-angiogenic,<sup>24,25</sup> anti-metastatic,<sup>14</sup> and even anticancer<sup>25-27</sup> effects in animals.

## 15d-PGJ<sub>2</sub> regulates adipocyte differentiation and osteoblast differentiation via a PPAR $\gamma$ -dependent pathway

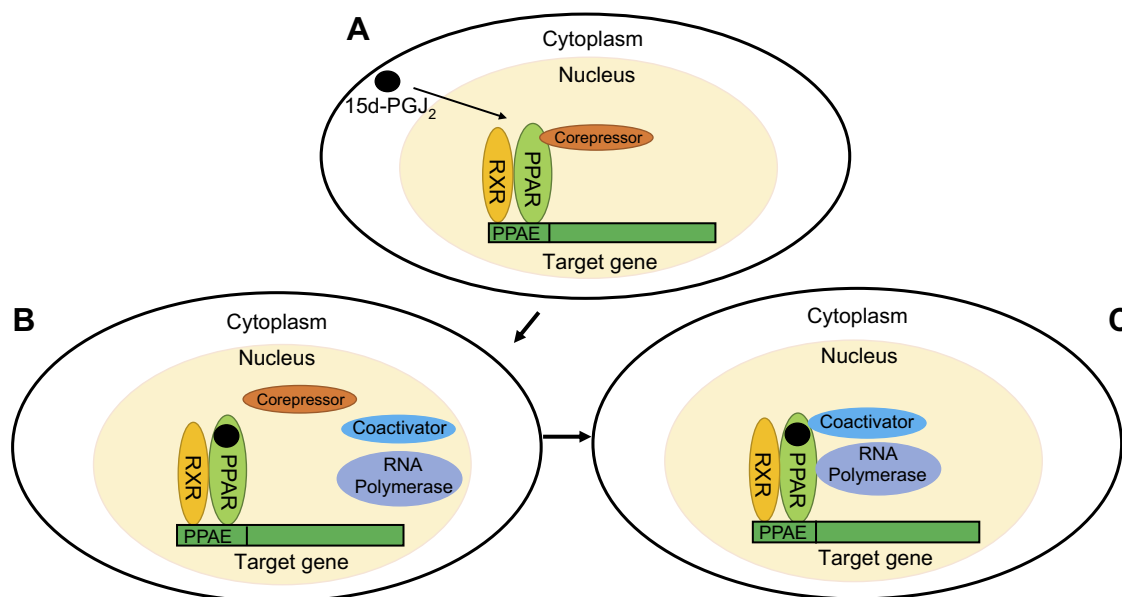
MSCs in the bone marrow are capable of differentiating into a variety of cell types, such as osteoblasts, adipocytes, chondrocytes, fibroblasts, or myocytes.<sup>5</sup> Each phenotypic transition requires a rigid, uninterrupted, and asynchronous program of gene expression.<sup>3</sup> Osteoblasts are involved in the construction of the organic and inorganic components of bone.<sup>28</sup> Recent gene deletion studies have shown that osteoblast differentiation requires a complex sequence of processes to activate transcription factors involved in

osteoblastogenesis (including Wnt/ $\beta$ -catenin, Runt-related transcription factor 2 (Runx2), and Osterix) and to suppress transcription factors involved in adipogenesis (including PPAR $\gamma$  and CCAAT/enhancer binding protein (C/EBP)).<sup>11,29</sup> The key factors in the process of MSC adipogenic and osteogenic lineage differentiation are PPAR $\gamma$  and Wnt, respectively.<sup>11</sup>

PPAR $\gamma$ , which acts as a nuclear receptor, contains a central DNA-binding domain and a C-terminal ligand-binding domain.<sup>30</sup> Under the strict regulation of many transcription factors such as PPAR $\gamma$  and C/EBP $\alpha/\beta/\delta$ , adipogenesis is achieved.<sup>31</sup> Numerous studies have shown that after 15d-PGJ<sub>2</sub> binds to PPAR $\gamma$ , transcription begins with the involvement of coregulators called corepressors and coactivators.<sup>9,10</sup> When 15d-PGJ<sub>2</sub> is absent, PPAR $\gamma$  forms a protein complex with corepressors such as silencing mediator for retinoid or thyroid-hormone receptors (SMRT), NCoR, and histone deacetylases, which transcriptionally silence PPAR $\gamma$ .<sup>32</sup> Upon 15d-PGJ<sub>2</sub> binding, corepressors dissociate from the heterodimer of PPAR $\gamma$  and retinoid X receptor (RXR) that were previously bound to DNA sequences in the promoter regions (called PPAR-response elements (PPRE)), thereby allowing PPAR $\gamma$  to recruit coactivators and initiate the transcription of adipocyte genes.<sup>33</sup> With or without ligand binding, PPAR $\gamma$  still binds to target genes (Figure 2).<sup>34</sup> The process

of PPAR $\gamma$  regulation of target gene expression is regulated by histone modification.<sup>35</sup> Research has shown that the transcriptional activity of PPAR $\gamma$  is inhibited by phosphorylation of serine residue 112 on the N terminus<sup>31</sup> and SUMOylation of lysine 107.<sup>36</sup> Nocturnin is a circadian-regulated protein that has been shown to control preadipocyte differentiation and regulate lipid metabolism through the modulation of PPAR $\gamma$  activity.<sup>37</sup> 15d-PGJ<sub>2</sub> is an endogenous natural ligand for PPAR $\gamma$  that regulates adipocyte differentiation by activating PPAR $\gamma$ , and coregulators that affect the expression of PPAR $\gamma$  may also regulate this process. These studies indirectly indicate that 15d-PGJ<sub>2</sub> is a potential regulator of bone marrow adipocyte differentiation via a PPAR $\gamma$ -dependent pathway.

Emerging evidence suggests that Wnt ligands play a role in promoting osteoblastogenesis through canonical and noncanonical signaling pathways.<sup>13,38</sup> The Wnt/ $\beta$ -catenin signaling pathway, commonly known as the canonical pathway, inhibits the formation of adipocytes by reducing the expression of PPAR $\gamma$  and C/EBP $\alpha$  mRNA.<sup>39,40</sup> Wnt5a acts as a noncanonical Wnt ligand to suppresses adipogenesis by inhibiting the transcriptional activity of PPAR $\gamma$  and subsequently activating the histone methyltransferase SETDB1.<sup>11</sup> Studies have also found that PPAR $\gamma$  deficiency induces osteoblastogenesis resulting in an increase in bone mass.<sup>41</sup> Adipocyte differentiation and



**Figure 2** Regulation of target gene expression by binding of 15d-PGJ<sub>2</sub> to PPAR $\gamma$ . (A) PPAR $\gamma$  forms a heterodimer with RXR to recognize PPRE in the promoter region of target genes. When the PPAR $\gamma$  ligand is absent, PPAR $\gamma$  forms a protein complex with corepressors, thus transcriptionally silencing PPAR $\gamma$ . (B) 15d-PGJ<sub>2</sub> is an endogenous ligand for PPAR $\gamma$  that binds to PPAR $\gamma$  resulting in PPAR $\gamma$  dissociation from a corepressor. (C) Upon binding of 15d-PGJ<sub>2</sub> to the natural ligand, PPAR $\gamma$  can recruit coactivators and RNA polymerase to stimulate transcription of target genes.

**Abbreviations:** RXR, retinoid X receptor; PPRE, PPAR-response elements.

osteoblast differentiation are affected by both the PPAR $\gamma$  and Wnt pathways, and 15d-PGJ<sub>2</sub>, an endogenous ligand for PPAR $\gamma$ , is also involved in this regulatory process (Figure 3). These findings indicate that 15d-PGJ<sub>2</sub> promotes bone marrow adipogenesis and inhibits osteoblastogenesis via a PPAR $\gamma$ -dependent pathway, thereby reducing bone formation in bone metabolism.

## Role of 15d-PGJ<sub>2</sub> in osteoporosis

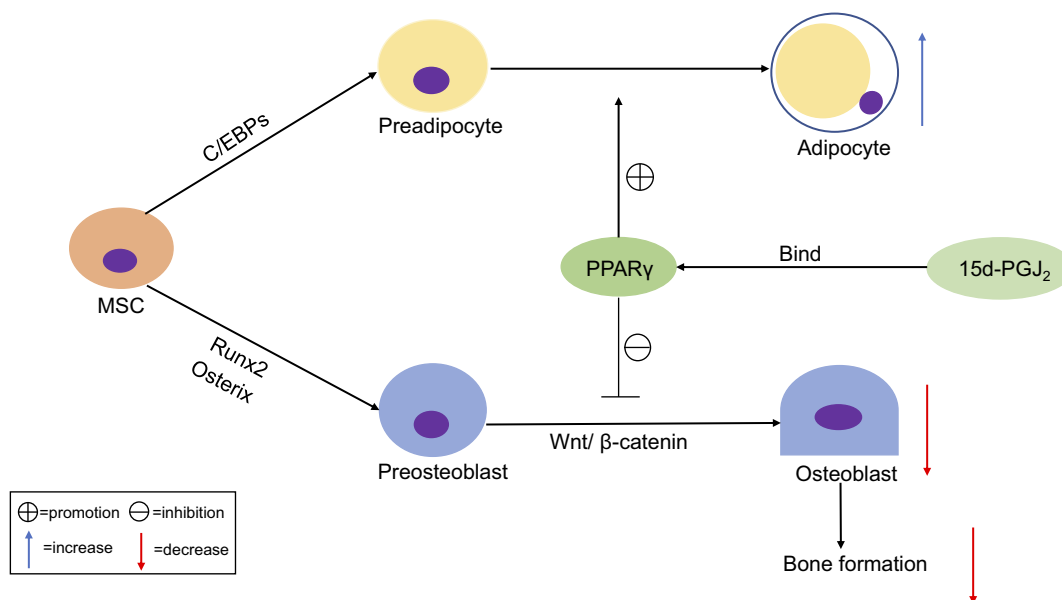
Osteoporosis is a serious social problem whose underlying mechanism is an imbalance between bone formation and bone resorption that increases the propensity of fragility fractures.<sup>42</sup> Osteoporosis has multiple risk factors, including old age, menopause in women, long-term use of glucocorticoids, a history of fragility fractures, and a history of smoking.<sup>42,43</sup> The imbalance between adipogenesis and osteoblastogenesis in the pathogenesis of primary or secondary osteoporosis may be related to the activation of PPAR $\gamma$ .<sup>41,44–46</sup>

Studies have shown that the expression of PPAR $\gamma$  in the bone marrow microenvironment increases with age.<sup>46</sup> Between 20 and 65 years of age, the trabecular volume decreased by 10%, while the volume of adipose tissue increased by 45%.<sup>47</sup> In the third decade of human life, adipose tissue occupies the femoral cavity, and in the seventh or eighth decade, fat can occupy the vertebrae.<sup>48</sup> An increasing number of studies have confirmed that the application of

glucocorticoids produces significant intramedullary fatty infiltration.<sup>49</sup> Research has shown that glucocorticoids stimulate the differentiation of MSCs into adipocytes and promote the accumulation of fat by decreasing the expression of type I collagen and osteocalcin mRNA, thereby inhibiting osteoblast differentiation.<sup>50</sup> Li et al<sup>51</sup> demonstrated that glucocorticoids reduced Cbfa1/Runx2 gene expression by 50–60%, while PPAR $\gamma$  gene expression was increased by 200%.

In one study, Guo et al<sup>52</sup> demonstrated that estrogen inhibited the formation of osteoclasts and bone resorption via microRNA-27a targeting of PPAR $\gamma$ . This study also showed that in postmenopausal women, estrogen deficiency reduced microRNA-27a expression and increased PPAR $\gamma$  expression, which in turn leads to loss of bone mass and even osteoporosis.<sup>52</sup> These studies indicate that PPAR $\gamma$  is highly expressed in age-related osteoporosis, glucocorticoid-induced osteoporosis, and postmenopausal osteoporosis, and its activators promote adipogenesis and inhibit osteoblastogenesis.<sup>46,51,52</sup>

Bisphosphonate is an important drug for the prevention and treatment of osteoporosis in clinical applications.<sup>53</sup> Bisphosphonates not only inhibit bone resorption by directly inhibiting mineral dissolution but also inhibit cell viability by directly acting on osteoclasts and interfering with specific cellular biochemical processes.<sup>53</sup> Studies have shown that ligand-activated PPAR $\gamma$  leads to



**Figure 3** 15d-PGJ<sub>2</sub> regulates adipocyte differentiation and osteoblast differentiation via a PPAR $\gamma$ -dependent pathway. MSCs have the potential to differentiate towards adipocytes and osteoblasts, through multiple factors and extracellular signaling pathways. Adipogenesis occurs under the strict regulation of multiple transcription factors, including PPAR $\gamma$  and C/EBPs, and osteoblastogenesis occurs under the regulation of Runx2, Osterix, and Wnt/ $\beta$ -catenin. Activation of PPAR $\gamma$  by 15d-PGJ<sub>2</sub> and other synthetic ligands can promote adipogenesis but suppress osteoblastogenesis, resulting in the inhibition of bone formation.

**Abbreviations:** MSCs, mesenchymal stem cells; C/EBPs, CCAAT/enhancer binding proteins; Runx2, runt-related transcription factor 2.

osteoporosis by promoting adipocyte differentiation and inhibiting osteoblast differentiation.<sup>51,52</sup> In vivo, 15d-PGJ<sub>2</sub>, as an endogenous ligand for PPAR $\gamma$ , may have an important regulatory role in the pathogenesis of osteoporosis in the absence of PPAR $\gamma$  synthetic agonists. However, research on the therapeutic advantages of 15d-PGJ<sub>2</sub> compared with traditional drugs is limited.

## 15d-PGJ<sub>2</sub> regulates osteoclast differentiation via PPAR $\gamma$ -independent and/or PPAR $\gamma$ -dependent pathways

Osteoclasts are involved in the removal of organic and inorganic bone components.<sup>29</sup> Receptor activator of NF- $\kappa$ B ligand (RANKL) regulates the activity of osteoclasts by binding to receptor activator of NF- $\kappa$ B (RANK) on its surface.<sup>54</sup> Osteoprotegerin (OPG) is a decoy receptor for RANKL and belongs to the tumor necrosis factor (TNF) receptor superfamily, which blocks the effects of RANKL.<sup>54</sup> Differentiation of osteoclasts requires coordinated regulation of transcription factors such as c-fos, c-jun and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1).<sup>1</sup> Studies have shown that OPG does not inhibit the process by which TNF- $\alpha$  promotes the formation of osteoclasts in humans.<sup>55</sup> In one study, Hounoki et al<sup>56</sup> found that 15d-PGJ<sub>2</sub> inhibited osteoclast differentiation induced by TNF- $\alpha$  through the PPAR $\gamma$ -independent pathway. 15d-PGJ<sub>2</sub> and ciglitazone, both of which are PPAR $\gamma$  agonists, were found to inhibit TNF-mediated osteoclast differentiation. The addition of the PPAR $\gamma$  antagonist, GW9662, to the culture rescued the inhibition induced by ciglitazone, but did not affect the inhibition induced by 15d-PGJ<sub>2</sub>.<sup>56</sup> RANKL-induced monocyte chemoattractant protein-1 (MCP-1) has been shown to play an important role in osteoclast differentiation.<sup>57</sup> In this study, 15d-PGJ<sub>2</sub> reduced MCP-1, thereby inhibiting osteoclast differentiation induced by TNF- $\alpha$ .<sup>57</sup> Considering the pivotal role of TNF- $\alpha$  in inflammatory joints, 15d-PGJ<sub>2</sub> appears to be a promising targeting factor for the treatment of inflammatory bone resorption diseases such as rheumatoid arthritis (RA).<sup>58</sup> A series of studies have shown that 15d-PGJ<sub>2</sub> may play an important role in osteoclast differentiation via a PPAR $\gamma$ -independent pathway, whereas ciglitazone acts via a PPAR $\gamma$ -dependent pathway.

## 15d-PGJ<sub>2</sub> is an important inflammatory mediator in RA

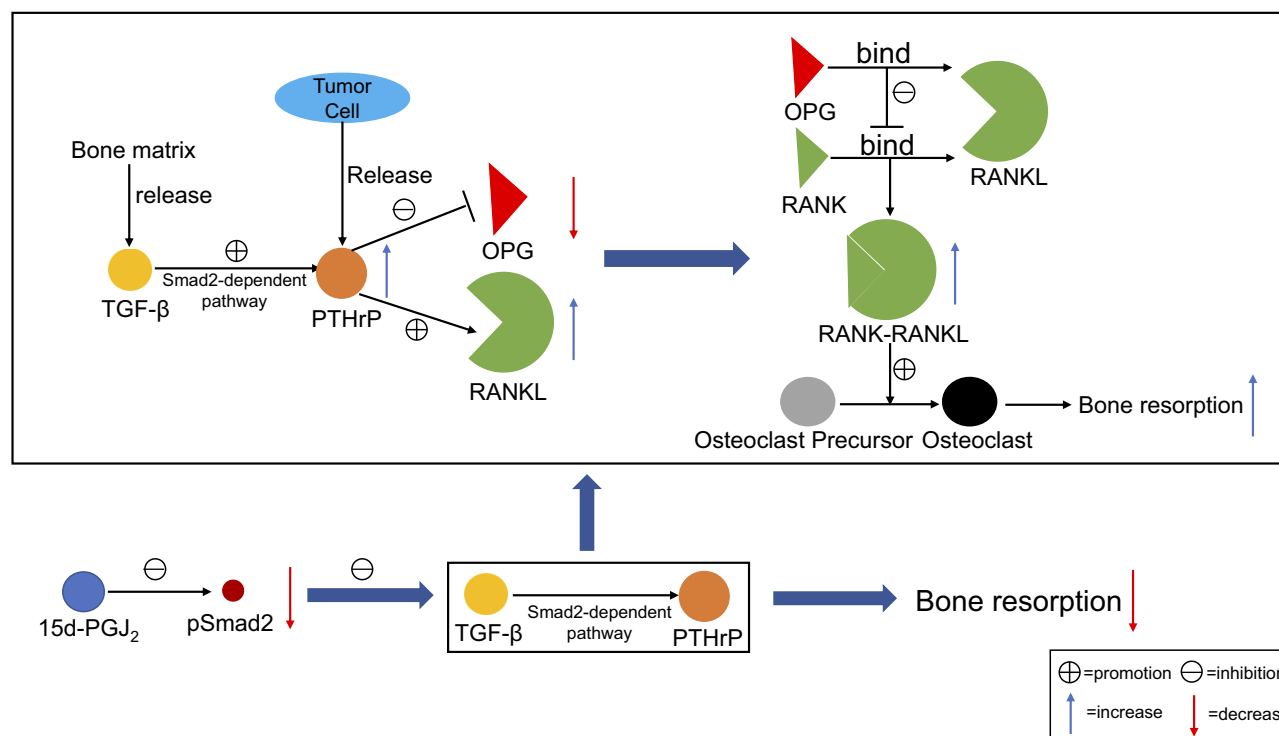
RA is a chronic disease affecting multiple joints that is accompanied by inflammation, massive synovial membranes, and

neovascularization.<sup>59</sup> PGE<sub>2</sub> plays an important regulatory role in RA by inducing joint erosion and synovial inflammation.<sup>60</sup> 15d-PGJ<sub>2</sub> is also a key negative regulator of the AA metabolism pathway and exerts an anti-inflammatory effect.<sup>15</sup> An earlier clinical study in 2001 showed that 15d-PGJ<sub>2</sub> inhibited the synthesis of PGE<sub>2</sub> induced by interleukin-1 (IL)-1 $\beta$  in rheumatoid synovial fibroblasts by downregulating COX-2 and cPLA<sub>2</sub> expression.<sup>61</sup> 15d-PGJ<sub>2</sub> has been suggested to be an important inflammatory mediator with potential for the treatment of RA.<sup>23</sup> The accumulated data suggest that 15d-PGJ<sub>2</sub> and a portion of synthetic PPAR $\gamma$  agonists inhibit inflammation in models of arthritis,<sup>23</sup> inflammatory bowel disease,<sup>62</sup> ischemia-reperfusion injury,<sup>63</sup> lupus nephritis,<sup>64</sup> and Alzheimer's disease.<sup>65</sup>

The anti-inflammatory activity of 15d-PGJ<sub>2</sub> has been proven in many studies, but some studies have also found it to have pro-inflammatory properties.<sup>15,66,67</sup> Glucocorticoids have also had a crucial role in the regression of inflammation through the intracellular glucocorticoid receptor (GR).<sup>68</sup> Recent studies have shown that 15d-PGJ<sub>2</sub> transiently attenuates GR signaling in monocytes/macrophages through a mechanism that relies on the interaction of the cyclopentenone ring in 15d-PGJ<sub>2</sub> with a cysteine residue in the components of the GR activation pathway.<sup>66</sup> The regulation of GR sensitivity by 15d-PGJ<sub>2</sub> requires the participation of SUMOylation.<sup>67</sup> The effect of the pro-inflammatory properties of 15d-PGJ<sub>2</sub> on the therapeutic effect of AA still requires further study.

## Role of 15d-PGJ<sub>2</sub> in bone tumors

Bone metastasis is a type of cancer metastasis that results from primary tumor invasion to the bone, mainly osteolytic metastasis, which leads to an imbalance in bone metabolism.<sup>69</sup> Breast cancer can metastasize to the bone, causing bone damage and ultimately leading to bone loss.<sup>70</sup> In one study, Kim et al<sup>14</sup> found that through a PPAR $\gamma$ -independent pathway, 15d-PGJ<sub>2</sub> dose-dependently inhibited the RANKL/OPG ratio and osteoclast differentiation, which in turn reduced the formation of absorbed pits by inhibiting the activities of cathepsin K and matrix metalloproteinase (MMP)-2/9 (Figure 4). Osteolytic factors derived from breast cancer cells include parathyroid hormone-related protein (PTHrP) and some interleukins (mainly IL-6, IL-8).<sup>69,71</sup> PTHrP enhances osteoclastogenesis and the activity of mature osteoclasts by upregulating RANKL and downregulating OPG in osteoblasts.<sup>69,72</sup> OPG regulates bone resorption by inhibiting osteoclast activation and final differentiation and by inducing apoptosis in osteoclasts.<sup>73</sup> Previous studies showed that transforming



**Figure 4** Regulation of 15d-PGJ<sub>2</sub> in bone metastasis of breast cancer. TGF-β is released from the bone matrix. PTHrP is an osteolytic factor derived from breast cancer cells. TGF-β increases the expression of PTHrP via Smad-dependent or Smad-independent pathways. PTHrP enhances osteoclastogenesis by upregulating RANKL and downregulating OPG in osteoblasts. Studies have shown that 15d-PGJ<sub>2</sub> inhibits PTHrP production via PPARγ-independent and Smad2-dependent pathways, thereby regulating osteolytic metastasis. This reduces the RANKL/OPG ratio and is beneficial for increasing the formation of osteoclasts. OPG is a decoy receptor for RANKL, which inhibits the association of RANK and RANKL, thereby inhibiting the production of RANK-RANKL. 15d-PGJ<sub>2</sub> reduces the production of RANK-RANKL, thereby inhibiting the differentiation of osteoclast progenitor cells into osteoclasts and, ultimately, reducing bone resorption.

**Abbreviations:** TGF-β, transforming growth factor β; PTHrP, parathyroid hormone-related protein; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin.

growth factor β (TGF-β) produced by the bone matrix increased the expression of PTHrP via Smad-dependent or Smad-independent pathways and was responsible for osteolytic lesions in breast cancer.<sup>74,75</sup> Studies have also shown that application of 15d-PGJ<sub>2</sub> inhibited significant enhancement of Smad2 phosphorylation as well as the nuclear levels of pSmad2 in TGF-β-stimulated cells.<sup>14,76</sup> The addition of GW9662 to the culture media did not rescue the inhibition of PTHrP by 15d-PGJ<sub>2</sub> regardless of TGF stimulation.<sup>14</sup> These results indicate that 15d-PGJ<sub>2</sub> inhibits PTHrP production via PPARγ-independent and Smad2-dependent pathways, thereby regulating osteolytic metastasis.

Common therapeutic agents for bone metastasis include denosumab and bisphosphonates.<sup>77</sup> Denosumab is a fully human anti-RANKL IgG2 antibody that inhibits the interaction between RANKL and RANK, thereby reducing the maturation and activity of osteoclasts.<sup>78</sup> Bisphosphonates are defined as “nitrogen-containing” (N-BPs: zoledronate, ibandronate) or “non-nitrogen-containing” (non-N-BPs: clodronate, etidronate).<sup>77</sup> The former is essential for the survival and activity of osteoclasts, while

the latter’s metabolites induce osteoclast apoptosis.<sup>78</sup> 15d-PGJ<sub>2</sub> affects osteoclastogenesis by reducing the production of PTHrP via a PPARγ-independent pathway. Denosumab and bisphosphonates act through anti-RANKL and target osteoclasts, respectively.<sup>77,78</sup> However, there is limited research on the therapeutic advantages of 15d-PGJ<sub>2</sub> compared with traditional drugs.

Osteosarcoma is a type of malignant tumor with a low survival that is uncommon and usually affects young people.<sup>79</sup> A low patient survival rate may be associated with the high metastatic potential of cancer.<sup>80</sup> However, the specific mechanisms that influence the progression and development of osteosarcoma are largely unknown. COX-2, which has pro-inflammatory activity, is highly expressed in primary osteosarcoma.<sup>81</sup> Recent studies have shown that COX-2 promotes cell migration, invasion, and proliferation in human osteosarcoma cells.<sup>81,82</sup> In one study, Kitz et al<sup>80</sup> found that 15d-PGJ<sub>2</sub> stimulates the expression of COX-2 via both the p38 and p42/44 mitogen-activated protein kinase (MAPK) and PPARγ-independent signaling pathways. Polo-like kinase 1 (PLK1) is an important cell cycle

regulator and a potential target for osteosarcoma.<sup>83</sup> In another study, Yen et al<sup>84</sup> found that 15d-PGJ<sub>2</sub> promotes apoptosis through reactive oxygen species (ROS)-mediated JNK activation, which may downregulate p-Akt and protein kinase A (PKA)–PLK1 pathways. Thus, 15d-PGJ<sub>2</sub> is a regulator of osteosarcoma and exerts cytotoxic effects through AKT and PKA-PLK1 inhibition.<sup>84</sup> From these studies, it was concluded that 15d-PGJ<sub>2</sub> is a potential regulator of osteosarcoma through the PPAR $\gamma$ -dependent pathway.

## Conclusion

Bone metabolism is an uninterrupted process that continuously removes old bone tissue and forms new bone tissue.<sup>28</sup> Inhibition of osteoblast differentiation or enhancement of osteoclast differentiation will lead to osteoporosis, which in turn can lead to osteopetrosis.<sup>3</sup> As an endogenous ligand for PPAR $\gamma$ , the cyclopentenone prostaglandin 15d-PGJ<sub>2</sub> plays an important regulatory role in metabolic bone diseases, RA and bone tumors through PPAR $\gamma$ -dependent and independent pathways.<sup>9,14,23</sup> It has been shown that through a PPAR $\gamma$ -dependent pathway, 15d-PGJ<sub>2</sub> stimulates the differentiation of preadipocytes into adipocytes in a cell culture model system, thereby inhibiting osteoblast differentiation and affecting bone formation in bone metabolism.<sup>9,10</sup> Many drugs with lipid-lowering effects have been used to treat the 15d-PGJ<sub>2</sub> pathway for bone metabolism. For example, Li et al<sup>85</sup> found that lovastatin decreased the expression of PPAR $\gamma$  but increased Cbfa1/Runx2 gene expression, causing transformation of the unformed osteoprogenitor cells from the adipocyte differentiation pathway to the osteoblast differentiation pathway. In one study, Jiang et al<sup>86</sup> demonstrated that pravastatin alleviated steroid-induced osteonecrosis in rats by activating the Wnt signaling pathway and inhibiting PPAR $\gamma$  expression. Studies have shown that tanshinol reduces bone formation damage by inhibiting adipogenesis via PPAR $\gamma$  signaling in glucocorticoid-induced osteoporosis rats.<sup>87</sup> This approach may be an attractive strategy to target osteoblastic cells by specific PPAR $\gamma$  inhibitors to treat bone diseases. The effect of 15d-PGJ<sub>2</sub> in promoting adipocyte differentiation and inhibiting osteoclast differentiation through a PPAR $\gamma$ -dependent pathway is also affected by these PPAR $\gamma$  inhibitors. The above studies conclude that 15d-PGJ<sub>2</sub> plays an important regulatory role in RA, osteosarcoma, and bone metastases via a PPAR $\gamma$ -independent pathway.<sup>14,23,80</sup> Understanding the underlying mechanisms responsible for controlling the balance between osteoclastogenesis and osteoblastogenesis in human is important for regulating bone metabolism. Finally, this review summarizes

the advances in the potential regulation of 15d-PGJ<sub>2</sub> in bone metabolism and provides new therapeutic targets for osteoporosis, bone tumors, and other bone diseases.

## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Zhencheng Xiong and Pan Luo are co-first authors.

## Disclosure

The authors report no conflicts of interest in this work.

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