Mod Rheumatol (2011) 21:1–9
DOI 10.1007/s10165-010-0347-x

REVIEW ARTICLE

Peroxisome proliferator-activated receptor gamma in osteoarthritis

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Received: 12 January 2010 / Accepted: 30 July 2010 / Published online: 4 September 2010

Abstract Osteoarthritis (OA) is among the most prevalent chronic human health disorders and the most common form of arthritis. It is a leading cause of disability in developed countries. This disease is characterized by cartilage deterioration, synovitis, and remodeling of the subchondral bone. There is not yet a satisfactory treatment to stop or arrest this disease process. Although several candidates for therapeutic approaches have been put forward, recent studies suggest that activation of the transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) is an interesting target for this disease. PPARγ is a ligand-activated transcription factor and member of the nuclear receptor superfamily. Agonists of PPARγ inhibit inflammation and reduce synthesis of cartilage degradation products both in vitro and in vivo, and reduce the development/progression of cartilage lesions in OA animal models. This review will highlight the recent experimental studies on the presence of PPARγ in articular tissues and its effect on inflammatory and catabolic responses in chondrocytes and synovial fibroblasts, as well as the protective effects of PPARγ ligands in arthritis experimental models. Finally, the role of PPARγ polymorphism in the pathogenesis of OA and related musculoskeletal diseases will also be discussed.

Keywords Cartilage · Chondrocytes · Osteoarthritis · PPAR gamma · Synovial fibroblasts

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Introduction

The most frequent musculoskeletal disorder and the most frequently diagnosed chronic medical arthritis condition worldwide is osteoarthritis (OA). This disease affects about 15% of the general population and the majority (60%) of people in the second half of their lifespan. It has higher prevalence in women when compared with men. It can induce a significant level of morbidity and represents an increasing burden from a medical, social, and economical point of view.

Treatment of this disease is becoming a major medical issue with the aging of the world population. With the predicted increase in incidences of arthritis in the upcoming decades, the cost related to OA is quickly becoming a serious concern. The challenge to improve the effectiveness of OA treatment is of significant importance, and future treatment should reduce or stop the progression of the disease.

Several risk factors that can induce or accelerate the development of this disease have been identified. These include high body mass index, joint injury or instability, malalignment, and meniscal lesion/extrusion in the knee. These factors independently or together can induce structural changes in the joint tissues that are known characteristics of the disease.

Recent advances in this field of research have clearly shown the global involvement in OA of all the major tissues of the joint, namely cartilage, synovial membrane, and subchondral bone [1].

Cartilage deterioration and damage is a critical event in OA [2]. Typically, the articular cartilage is regarded as the primary diseased tissue, with increased destruction and insufficient tissue repair. During OA initiation and progression, chondrocytes can be stimulated by the

proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) to express cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and microsomal prostaglandin E synthase-1 (mPGES-1), as well as matrix metalloproteases (MMPs), which degrade the extracellular matrix components aggrecan and collagen, resulting in cartilage damage. Furthermore, during OA the expression of some anabolic factors is substantially downregulated, resulting in increased cartilage destruction.

Data also showed that synovial inflammation occurs in early OA and can be subclinical [3]. However, synovitis is evident at the clinical stage of the disease and could be the cause for a patient to see a physician. Synovitis is believed to be induced at first by the cartilage matrix proteolytic degradation products that produce wear particles and soluble cartilage-specific neo-antigens, as well as other factors including microcrystals and abnormal mechanical stress. These components are released into the synovial fluid and are phagocyted by synovial lining macrophages, perpetuating the inflammation of the synovial membrane through the synthesis of mediators. In turn, these mediators diffuse into the cartilage through the synovial fluid, and create a vicious circle, increasing cartilage degradation and subsequently producing more inflammation. In the synovial membrane, inflammatory mediators are synthesized by different cell populations, but data suggest that the synovial fibroblasts are the major cells to produce the catabolic factors during the disease process.

The existing treatments for this disease are palliative and only provide symptomatic relief without preventing the progression of the disease. The current pharmacological treatments include nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, additional new therapies are needed. Among the potential therapeutics, Peroxisome proliferator-activated receptor (PPARγ) is an attractive target for the treatment of OA.

This review will comprehensively define the role of PPARγ and its downstream signaling in cartilage and synovial membrane, and will further define the complex role of PPARγ in the joint structure alterations observed in OA. These reported data will not be limited to OA, as they could also be applied to other arthritis diseases such as rheumatoid arthritis (RA).

PPARγ

PPARs are members of the nuclear hormone receptor superfamily, which includes receptors for steroids, thyroid hormone, vitamin D, and retinoic acid. Three PPAR isoforms have been described: PPARα, PPARβ/δ, and PPARγ [4]. PPARα is mostly present in liver, heart, and muscle, where it is believed to play a role in the catabolism of fatty acid [5]. PPARβ/δ is ubiquitously expressed and plays important roles in various physiological processes, including lipid homeostasis, epidermal maturation, skin wound healing, and brain development [6, 7]. PPARγ is the most studied member of this family. PPARγ regulates gene expression by binding as a heterodimer with the retinoid X receptor (RXR). The PPARγ/RXR heterodimer binds to sequence-specific PPAR response elements in the promoter region of target genes and acts as a transcriptional regulator. Two PPARγ isoforms (PPARγ1 and 2) have been identified. They derive from the same gene, but their production results from the gene alternative promoter and differential messenger RNA (mRNA) splicing [8, 9]. Compared with PPARγ1, PPARγ2 has 30 additional amino acids at the amino-terminus [8, 9]. PPARγ1 is widely expressed in many tissues, including inflammatory and immune cells, whereas PPARγ2 is found mainly in adipose tissues. PPARγ plays important roles in the regulation of glucid and lipid metabolism, and has been implicated in several pathological conditions including diabetes [10], cardiovascular diseases [11], carcinogenesis [12], and inflammation [13–15]. Emerging evidence suggests that PPARγ plays an important role in the pathogenesis of arthritis, OA, and RA, and possibly other chronic inflammatory diseases.

PPARγ ligands

PPARγ can be activated by a variety of compounds that are classified as natural/physiologic or synthetic agonists. Natural agonists include the essential fatty acids arachidonic acid, docosahexanoic acid, and eicosapentanoic acid, and the 15-lipoxygenase metabolites, 13(*S*)-hydroxy octadecadienoic acid (13-HODE) and 15(*S*)-hydroxyeicosatetraenoic (15-HETE) [16, 17]. The cyclopentanone prostaglandin 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) was the first endogenous agonist for PPARγ to be identified [16, 18] and has been widely used as a pharmacological tool to define the role of PPARγ. The unsaturated fatty acid derivative nitrolinoleic acid (LNO_2), generated via nitric oxide (NO)-dependent oxidative inflammatory reactions, has also been reported to activate PPARγ [19].

A wide range of synthetic compounds bind to and activate PPARγ, including the antidiabetic thiazolidinediones, also known as glitazones, such as troglitazone, pioglitazone, ciglitazone, and rosiglitazone [20, 21]. Troglitazone and rosiglitazone were withdrawn from the market because of hepatotoxicity and heart risks, respectively. Several NSAIDs, such as indomethacin, ibuprofen, fenoprofen, and flufenamic acid, were also reported to bind and to activate PPARγ [22]. Recently, a novel family of dual-acting PPARα/γ agonists has been developed: glitazars including muraglitazar, tesaglitazar, and farglitazar are being evaluated

for treatment of type 2 diabetes and complications associated with this disease [23].

PPARγ in chondrocytes

Among the two PPARγ isoforms, human cartilage predominantly expresses PPARγ1, and the expression level of this isoform is reduced in OA compared with normal cartilage [24]. This finding suggests that reduced PPARγ expression in OA cartilage may reflect increased expression of inflammatory and catabolic factors. Hence, in human OA chondrocytes, treatment with IL-1β resulted in a decrease in PPARγ protein expression [24]. TNF-α, IL-17, and prostaglandin (PG)E_2 also downregulated PPARγ1 expression [24]. Inhibitors of the mitogen-activated protein kinases (MAPK), p38 (SB203580), and c-Jun N-terminal kinase (JNK) (SP600125), and of nuclear factor (NF)-κB signaling [SN-50, MG-132, and cafeic acid phenethyl ester (CAPE)] abolished IL-1β-induced downregulation of PPARγ1 expression [24]. Similarly, IL-1 reduced PPARγ protein expression in normal rat chondrocytes [25]. Thus, inhibition of PPARγ expression in chondrocytes by proinflammatory cytokines may be an important process in OA pathophysiology. PPARγ expression was also reduced in cartilage from a rat model of mono-iodoacetate-induced OA compared with controls [26]. As this model does not involve inflammatory pathways, the effects of PPARγ could be related to other degradative factors involved in this disease.

Effects of PPARγ agonist on chondrocytes

Anti-inflammatory effects

Several studies have shown that PPARγ is expressed and functional in chondrocytes and that PPARγ agonists downregulate inflammatory responses in these cells. For instance, treatment of human OA chondrocytes with 15d-PGJ_2 or troglitazone suppressed IL-1β-induced NO and PGE_2 production as well as iNOS and COX-2 expression [27–29]. Moreover, the induction of NO production by the inflammatory cytokines IL-17 and TNF-α was also prevented upon PPARγ activation. The use of synthetic promoters with multimerized copies of transcription factor binding sites revealed that this inhibition takes place at the transcriptional level by interfering with activator protein AP-1 and NF-κB activities [27–29]. In rat chondrocytes, treatment with 15d-PGJ_2 prevented IL-1β-induced iNOS and COX-2 expression as well as the production of NO and PGE_2 [25, 30].

In addition, 15d-PGJ_2 inhibited the induction of mPGES-1, which catalyzes the terminal step in PGE_2 synthesis in both human OA [31] and rat chondrocytes [32, 33].

Anti-matrix metalloprotease (MMP) effects

Effects of 15d-PGJ_2

Increased production of MMPs plays a critical role in cartilage degradation during the OA process. PPARγ activation was shown to suppress the production of several MMPs and to prevent proteoglycan degradation [27, 34–36]. In human OA chondrocytes, 15d-PGJ_2 and troglitazone blocked IL-1β-induced MMP-13 expression by inhibiting the AP-1 and NF-κB pathways [27]. Similarly, in rabbit chondrocytes, rosiglitazone blocked IL-1β-induced MMP-1 production through DNA binding competition on the composite PPRE/AP1 site in the MMP-1 promoter [34]. In rat chondrocytes, 15d-PGJ_2 and GI262570 (an agonist of PPARγ) inhibited IL-1β- and TNF-α-induced MMP-3 and MMP-9 as well as proteoglycan degradation [35]. More recently, Mix et al. [36] demonstrated that 15d-PGJ_2 and the synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) suppress MMP-1 and MMP-13 in the human chondrocytic cell line SW1353.

Anti-apoptotic effects

Inhibition of chondrocyte apoptosis is a potential therapeutic approach to prevent cartilage degradation in OA. Interestingly, 15d-PGJ_2 and its precursor PGD_2 were shown to prevent the induction of apoptosis in normal human articular chondrocytes by the NF-κB inhibitor Bay 11-7085. This appears to occur through the inhibition of the MAPK ERK-1/2 pathway [37]. In contrast, Shan et al. [38] reported that 15d-PGJ_2 induced apoptosis in normal, OA, and RA human chondrocytes through activation of the p53 and caspase cascades. Reasons for these discrepancies are unclear but may reflect differences in experimental conditions.

Effects of other natural PPARγ activators

The lipids 13-HODE and 15-HETE are potent PPARγ activators [17]. Biosynthesis of 13-HODE and 15-HETE is catalyzed by 15-lipoxygenase (15-LOX). 15-LOX exists in two isoforms, 15-LOX-1 and -2. 15-LOX-1 preferentially converts linoleic acid to 13-HODE, and 15-LOX-2 metabolizes arachidonic acid to 15-HETE [39, 40]. Data suggest that 15-LOX may have a potential role in preventing the cartilage destruction seen in arthritis. Indeed, human OA chondrocytes express both 15-LOX isoforms, and 13-HODE and 15-HETE dose-dependently suppressed IL-1β-induced MMP-1 and MMP-13 expression [41].

Moreover, these factors also decreased the degradation of type II collagen in IL-1β-treated human OA cartilage explants [41]. Interestingly, pretreatment with the PPARγ antagonist GW9662 prevented the suppressive effect of 13-HODE and 15-HETE, suggesting that their effects are mediated by PPARγ [41].

15d-PGJ_2 is generated through dehydration of PGD_2, biosynthesis of which is catalyzed by two PGD synthases (PGDS): lipocalin PGDS (L-PGDS) and hematopoietic-type PGDS (H-PGDS). L-PGDS is glutathione independent whereas H-PGDS is glutathione dependent [42]. L-PGDS (also called β-trace) belongs to the lipocalin family, a group of secretory proteins that transport small hydrophobic molecules such as retinoids [43] and gangliosides [44]. Investigation of the expression of PGDS in human cartilage revealed the presence of both L- and H-PGDS, with L-PGDS being the predominant isoform [45]. The levels of L-PGDS were found elevated in human OA cartilage compared with normal. Moreover, in these cells, IL-1β enhanced the L-PGDS expression, a process which requires de novo protein synthesis and involves the JNK and p38 MAPK as well as NF-κB and Notch signaling cascades [45]. The L-PGDS metabolite PGD_2 also inhibited IL-1β-induced MMP-1 and MMP-13 production mediated through the DP1/cAMP/PKA pathway [45]. Given the anticatabolic properties of L-PGDS, it is tempting to speculate that its increased expression may be an attempt to counteract the IL-1β catabolic effects.

Effects of PPARγ agonists on synovial fibroblasts

15d-PGJ_2 and troglitazone inhibited the endogenous expression of several inflammatory and catabolic genes including IL-1β, TNF-α, IL-6, IL-8, and MMP-3 in human synovial fibroblasts from OA and RA patients [46, 47], and decreased lipopolysaccharide (LPS)-induced expression of iNOS, COX-2, IL-1β, and TNF-α in rat synovial fibroblasts [48]. The expression of MMP-1, COX-2, and mPGES-1 was also suppressed by 15d-PGJ_2 and troglitazone in IL-1β-treated OA synovial fibroblasts [49–51]. Tsubouchi et al. [52] demonstrated that 15d-PGJ_2, but not troglitazone, suppressed IL-1β-induced expression of cytosolic phospholipase A_2 ($cPLA_2$) and COX-2 as well as the production of PGE_2 in human RA synovial fibroblasts.

As with chondrocytes, the effect of PPARγ agonists on synovial fibroblast apoptosis remains to be further documented. Some studies demonstrated that 15d-PGJ_2 and troglitazone induce apoptosis in synovial fibroblast from RA patients [53, 54], whereas others reported that PPARγ activators had either no effect on apoptosis in RA synovial fibroblasts [46, 47] or prevented apoptosis in normal synovial fibroblasts [37].

Mechanisms of PPARγ-mediated suppression of gene expression

Several mechanisms have been proposed to explain transcriptional repression by PPARγ. First, PPARγ may suppress transcription by directly binding to key transcription factors and inhibiting their DNA binding and/or transcriptional activity. In this context, PPARγ has been shown to inhibit SP-1, NF-κB, and nuclear factor of activated T cells (NF-AT) transcriptional activity through mechanisms that involve protein–protein interactions [55, 56].

Secondly, there is also evidence that PPARγ can downregulate transcription by competing for general transcriptional co-activators that are important for the activity of several transcription factors. Indeed, PPARγ was shown to interact with several co-activators such as cyclic adenosine monophosphate (cAMP)-responsive element binding factor (CREB)-binding protein (CBP), p300, steroid receptor co-activator-1 (SRC-1), and thyroid hormone receptor-associated protein (TRAP220) [57, 58]. Importantly, these cofactors are required for the transcriptional activity of AP-1, NF-κB, early growth response-1 (Egr-1), signal transducers and activators of transcription (STAT), and NF-AT as well as enhancing their transcriptional activity. Thus, the sequestering of limited amounts of general transcriptional co-activators by activated PPARγ could account for the transcriptional repressive effect of PPARγ.

The acetylation of nucleosomal histones plays an important role in the regulation of gene transcription through the remodeling of chromatin structure [59, 60]. The histone acetylation status is controlled by the opposing actions of two classes of enzymes: histone acetyl transferases (HATs) and histone deacetylases (HDACs). Acetylation of histones at target promoters by HATs is commonly associated with transcriptional activation. In contrast, deacetylation of histones by HDACs is generally associated with transcriptional repression. For instance, the suppression of IL-1β-induced granulocyte macrophage colony-stimulating factor (GM-CSF) and IL-8 expression by the anti-inflammatory drugs dexamethasone and theophylline appears to be due to the recruitment of HDACs to these gene promoters and subsequent histone deacetylation [61, 62]. In human OA synovial fibroblasts the IL-1β induction of COX-2 is associated with the hyperacetylation of histone H3 and H4 at the COX-2 promoter [50], and treatment with 15d-PGJ_2 inhibits IL-1β-induced COX-2 expression as well as histone acetylation at the COX-2 promoter. However, the reduction of histone H3 acetylation does not correlate with recruitment of histone deacetylases (HDACs) to the COX-2 promoter, and pretreatment with a specific HDAC inhibitor, trichostatin A (TSA), did not relieve the suppressive effect of 15d-PGJ_2,

indicating that HDACs are not involved in the inhibitory effect of 15d-PGJ_2 on COX-2 transcription [50]. PPARγ was also shown to inhibit transcription by preventing the clearance of co-repressor complexes from target gene promoters [63]. Indeed, Pascual et al. [63] demonstrated that PPARγ activation results in a conformational change leading to the sumoylation of the ligand-binding domain of PPARγ by the E3 ligase PIAS1. Sumoylated PPARγ then binds to the nuclear receptor co-repressor (NCoR)-histone deacetylase-3 (HDAC3) complex and blocks its release from the promoter of inflammatory genes [63].

PPARγ in experimental models of arthritis

The in vivo protective effects of PPARγ agonists in OA have been further highlighted in two animal models. In an experimental guinea pig model of OA (partial medial meniscectomy), administration of pioglitazone dose-dependently reduced the size and the depth of cartilage lesions as well as their histologic severity [64]. The protective effect of pioglitazone was related to reduced expression of MMP-13 and IL-1β [64]. In a canine model of OA (anterior cruciate ligament transection), similar reduction in cartilage lesions was found [65]; this study further showed a reduction in the expression of MMP-1, iNOS, and a disintegrin and metalloproteinase domain with thrombospondin motifs (ADAMTS)-5 as well as a decrease in the activation of the signaling pathways ERK-1/2, p38, and NF-κB [65]. Thus, it seems that PPARγ agonists exert chondroprotective effects by impairing the expression of key genes involved in the pathogenesis of OA and the signaling pathways that mediate their transcriptional activation.

Protective effects of PPARγ activators have also been observed in RA animal models. Administration of the PPARγ agonists 15d-PGJ_2 and troglitazone suppressed pannus formation and mononuclear cell infiltration in rat adjuvant-induced arthritis [53]. In a mouse model of type II collagen-induced arthritis (CIA), treatment with rosiglitazone ameliorated the clinical signs and histologic features of the disease, and reduced plasma levels of the inflammatory cytokines IL-1β, TNF-α, and IL-6 [66]. This was further confirmed in a CIA rat model in which both pioglitazone and rosiglitazone reduced synovitis and the expression of IL-1β and TNF-α in this tissue [67]. However, although both compounds prevented bone erosions and inflammatory bone loss, they had no effect on cartilage lesions or proteoglycan content [67].

Other studies using the CIA model showed that the PPARγ agonists THR0921 [68] and CLX-090717 [69] reduced clinical disease activity as well as histological scores of joint destruction. Tomita et al. [68] further demonstrated that PPARγ activation impaired immune responses; treatment with THR0921 diminished the proliferation of spleen cells and the levels of circulating IgG antibodies to type II collagen, as well as the expression levels of TNF-α, IL-1β, monocyte chemotactic protein-1, and receptor activator of NF-κB ligand (RANKL) [68]. The protective effect of PPARγ activation was further strengthened by a study in which antigen-induced arthritis was exacerbated in mice heterozygous for PPARγ deficiency [70].

PPARγ polymorphism in OA

Several genetic variants in the PPARγ gene have been identified, the most prevalent being Pro12Ala and C161T (also referred to as C1431T). The Pro12Ala polymorphism results from a CCA-to-GCA missense mutation in codon 12 of exon B of the PPARγ gene. Since this mutation is located in the ligand-independent activation domain of the protein, it may cause conformational changes and consequently affect its transcriptional activity [71]. The Pro12Ala polymorphism has been associated with improved insulin sensitivity [72], reduced risk of type 2 diabetes [73], myocardial infarction [74], and atherosclerosis [75]. The silent C161T (C1431T) polymorphism in exon 6 has been associated with an increased plasma level of leptin [76], reduced risk of coronary artery disease [77], survival of patients with immunoglobulin A nephropathy [78], and longevity [79].

The influence of these two PPARγ polymorphisms, Pro12Ala and C161T, was assessed on the prevalence and severity of OA in a French Canadian population. Data revealed no significant difference in the frequency of either polymorphism between OA patients and controls [80]. There were also no significant differences after stratification of patients according to age at disease onset, or radiographic or functional severity. Similarly, haplotype analysis of both PPARγ polymorphisms showed no association with OA or its clinical features. These results suggest that these two common polymorphisms in the PPARγ gene are unlikely to confer susceptibility to OA in the French Canadian population. Further studies on other ethnic populations are needed to assess the role of these and other polymorphisms in the pathogenesis of OA.

In a Korean population of RA patients, El-Sohemy et al. [81] examined whether Pro12Ala was associated with susceptibility to this disease but did not find any association. However, Butt et al. [82] demonstrated a modest association between the Pro12Ala variant and psoriatic arthritis in a Caucasian population.

Various studies have also examined PPARγ polymorphisms in relation to bone mineral density (BMD). The results of these studies, however, were inconsistent. For

instance, an association between the PPARγ C161T polymorphism and reduced BMD was found in Japanese postmenopausal women [83, 84]. In contrast, there was no association between the PPARγ C161T polymorphism and BMD in premenopausal and postmenopausal Korean women [85] or postmenopausal Spanish women [86]. Reasons for such discrepancies could be related to the study design (insufficient statistical power), ethnic differences, and/or genetic heterogeneity.

Conclusions

At the present time, no disease-modifying treatment exists for OA. Investigating the pathophysiological mechanisms of the disease is an obvious priority. Research has already contributed to and will continue to play a part in the development and improvement of treatment strategies aimed at specifically and effectively slowing down or stopping the progression of the disease. Findings with regard to the physiological and pathological mechanisms have made it possible to better target therapeutic approaches that could lead to the development of such treatments.

Increased inflammatory and catabolic responses in chondrocytes and synovial fibroblasts are believed to contribute to the pathogenesis of OA as well as other chronic arthritic diseases. Defining the functional role of PPARγ has begun to bring new insight into the disease pathogenesis. In the last decade, there have been an increasing number of in vitro and in vivo studies showing that PPARγ agonists inhibit several catabolic and inflammatory responses, indicating their potential usefulness in the treatment of arthritis. Interestingly, PPARγ agonists of the thiazolidinediones class are currently used for treatment of type 2 diabetes and are in clinical trials for other pathological conditions including cancer and cardiovascular diseases.

Although the clinical trials presently ongoing should facilitate future studies assessing PPARγ agonists as anti-arthritic drugs, several issues need to be examined. In particular, it is important to better characterize the molecular mechanisms by which PPARγ agonists modulate gene expression in articular cells.

Acknowledgments The authors are grateful to Virginia Wallis for her assistance with manuscript preparation.

Conflict of interest None.

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