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The significance of peroxisome proliferator activated receptors PPAR-γ pathway in Arthritis

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ABSTRACT

PPAR – γ are members of a nuclear receptors superfamily located in various parts of the human body. They are implicated in many biochemical pathways and are shown to hold a key role in adipogenesis, adipose tissue differentiation and regulation of glucose levels, while also exhibiting anti-inflammatory properties. Furthermore, numerous studies have verified their implication in the process of cell differentiation and apoptosis. Over the last decade there has been ongoing interest and continuous investigation concerning their potential role on bone metabolism and the treatment of arthritis.

KEY WORDS: arthritis; cartilage; peroxisome proliferator activated receptors; pathways

1. Introduction

Peroxisome proliferator activated receptors (PPARs) are part of a nuclear receptor superfamily and can be separated into 3 subgroups: (a) PPARs-α, are usually detected at the liver, pancreas, lungs and kidneys, whilst there is also an abundance of PPAR-α receptors in muscle tissue and vascular wall cells. (b) PPARs-β/δ, are located at the human embryonic kidneys, small intestines, muscle and adipose tissue as well as the developing brain and heart. (c) PPARs-γ, are mostly found in white and brown adipose tissue, osteoclasts, synoviocytes, chondrocytes, macrophages, T-lymphocytes, the mammary and adrenal gland, skeletal muscle and prostate as well as the heart and type 2 alveolar pneumonocytes [1]. When triggered, PPARs-γ promote adipogenesis and adipocyte differentiation, while regulating glucose homeostasis. Furthermore,

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by suppressing NFκB, they exhibit anti-inflammatory action and promote cellular differentiation and apoptosis [2]. According to Ricotte et al. it is also possible that PPARs-γ trans-repress the expression of pro-inflammatory mediators by inhibiting STAT-1 (signal transducers and activators of transcription-1) and AP-1 (activation protein-1) signaling [3, 4]. Moreover, after studying human chondrocytes, Yamamoto et al. reported that it plays a critical role in the control of B cell response and diseases in which B cell hyper reactivity is involved, such as arthritis and autoimmunity [5].

Various pharmaceutical compounds such as Thiazolidinediones (TZDS), NSAIDS, prostanoids (15dPGJ2), leukotriene B4 (LTB4), 15-hydroxy-eicositetranoic acid (15-HETE), Non-Steroidal-Anti-Inflammatory Drugs (NSAIDs), eicosanoids, glitazars and fatty acids are among the identified PPAR-γ ligands. Despite their differences, all ligands have carboxylate moiety and lipophylic backbone [6]. However, Jee et al. reported that 15dPGJ2 had the greater PPAR-γ affinity being 5- to 30-fold more potent than TZDS [7], with troglitazone, indomethacin, fenoprofen and ibuprofen following [8].

2. The role of PPAR-γ in arthritis

Osteoarthritis (OA) and rheumatoid arthritis (RA) are associated with inflammation mediated by IL1β and TNFα. They consequently trigger the production of MMPs by chondrocytes and synovial fibroblasts [9] causing destruction of extracellular matrix components in both bone cartilage and tendons.

PPAR-γ ligands prevent joint destruction by either reducing the expression of inflammatory cytokines [10] or limiting the expression of MMPs [11]. In addition they hold an important role in the *in vitro* transformation of fibroblast like synovial cells (FLS) into adipocyte like cells [13]. In RA, FLS are the most common cell type at the pannus–cartilage junction and contribute to joint destruction through their production of cytokines, chemokines, and matrix-degrading molecules and by migrating and invading joint cartilage. They share some characteristics with malignant cells [14,10] and it has been suggested that after their differentiation into adipocyte like cells their proinflammatory character is diminished [13].

3. Degenerative arthritis

Osteoarthritis (OA) is a degenerative disease, highly associated with motor disability, resulting in degradation of the articular cartilage and declined life quality. Factors such as aging, excessive mechanical stress, traumatic injury and genetic susceptibility are major risk factors for the occurrence of osteoarthritis. The pathophysiology of this condition is related with a shift of balance between the production rate and the degradation of the human cartilage, possibly due to the induction of proteolysis. Excessive release and production of cytokines, matrix metalloproteinases (MMP's) and nitric oxide (NO) are playing an immense role in the occurrence of OA [12].

Cytokines IL-1b and TNFα induce the production of MMP1, 8 and 13.The latter are considered primary mediators of the joint destruction process by degrading type II collagen. Furthermore, IL-1b and TNF-α are responsible for the increased levels of NO. According to Clansy et al., NO can lead to cartilage degradation by 1) reducing the production of cartilage matrix, 2) enhancing the activity of MMP's, 3) inhibiting the IL1 receptor antagonist and 4) inducing chondrocyte apoptosis [15].

After studying guinea pigs suffering from experimental osteoarthritis Kobayashi et al. found that PPAR-γ ligand Pioglitazone caused dose-dependent decrease of MMP13 and IL-1b amounts situated in the osteoarthritic cartilage. This resulted in remission of osteoarthritic symptoms and decrease of the degenerative lesion's depth and size [16].

It has been asserted that COX-2 inhibitors can demonstrate biologic activities other than the simple inhibition of COX action and release of prostaglandins [17]. Therefore the effect of NSAIDS as PPAR-γ ligands was investigated and confirmed [5]. However, despite that confirmation, other studies showed that nimesulide and other PPAR-γ ligands such as 15fPGJ2 and ciglitazone, increase COX2 mRNA in dose dependent manner [18].

Curcumin is another PPAR gamma ligand that de-

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celerates osteoarthritis progression and offers adequate pain relieve. However, it remains unclear whether its action is related with the PPAR gamma pathway [19, 20].

Irrespective of the equivocal results of older studies it has been confirmed that PPARγ deficiency results in severe, accelerated osteoarthritis [21].

4. Acute gouty arthritis

Acute gouty arthritis is a monoarticular disease with excruciating symptoms and sudden onset. It is caused after the deposition of monosodium urate monohydrate (MSU) in the articular and periarticular tissue. MSU crystals infiltrate leucocytes and stimulate synovial cells through leucocyte secreted chemokines (IL-8, monocyte chemoatractant protein 1), oxygen radicals, cytokines (TNFα, IL-6, IL-1), arachidonic acid, metabolites and proteinases [22]. The activation of neutrophils after the MSU crystals sedimentation initiates the tissue damage, which is perceived as pain, edema and periarticular erythema.

MSU crystals induce monocyte PPAR-γ expression *in vitro* and in vivo, while PPAR-γ ligands decrease the production of crystal-induced cytokines. When tested, both 15dPGJ2 and indomethacin reduced significantly the production of cytokines. However, troglitazone failed to exert significant results. Those results imply that PPAR-γ may hold a significant biologic role in the self-limiting episodes of gouty arthritis [23].

5. Psoriatic arthritis

Psoriatic arthritis is a chronic disorder affecting both the joints and skin. It affects 5-7% of the population suffering from psoriasis and appears approximately 10 years after it is diagnosed. Dactylitis, tendinitis as well as joint inflammation and neovascularization are among its primary clinical manifestations. Its treatment does not differ from that of rheumatoid arthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used as treatment as well as Disease Modifying Antirheumatic Drugs (DMARDs) with the latter demonstrating inconsistent and unsatisfactory efficacy. Moreover, anti-TNF agents have limited use due to their high costs.

Activation of the PPAR-γ pathway had positive results in several *in vitro* and *in vivo* models (e.g. collagen-induced arthritis). Pioglitazone was used in most studies and exerted remarkable anti-inflammatory properties while suppressing neovascularization [24]. It could therefore be a promising treatment for psoriatic arthritis, even though more clinical studies are needed in order to define its response in patients with psoriasis and psoriatic arthritis [25].

6. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic polyarticular autoimmune relapsing and destructive disease affecting mainly diarthroidal joints. It is mainly associated with massive synovial cell proliferation, inflammation and angiogenesis [26, 27].

An antigen-dependent T cell activation stimulates mesenchymal and fibroblast-like synovial cell proliferation, causing irreversible damage in both bone and cartilage [28]. Therefore the rationale for the treatment of RA would be suppressing or blocking osteoblast and fibroblast mitogens such as prostaglandins, nitric oxide and cytokines (TNFα and IL-1b) that promote the production of other cytokines and the formation of hyperplasic synovium.

The concomitant use of the PPAR-γ agonist pioglitazone and methotrexate appears to be promising therapeutic strategy for rheumatoid arthritis patients [32]. Thiazolidinediones inhibit macrophage activation and contribute to the decrease of inflammatory cytokine expression and release in macrophages and monocytes. They also induced synoviocyte apoptosis and reduced secretion of TNF-α, IL-6 and IL-8 in synoviocytes of rheumatoid arthritis patients [29]. Tsubouchi Y et al., came to the same conclusion after investigating the anti-inflammatory effects of 15dPGJ2 and troglitazone as well as their impact on RA cell growth [30].

Apart from the above mentioned promising use of thiazolinediones, other studies confirmed that the activation of PPAR-γ caused by some NSAIDs may help prevent the degradation of articular cartilage in rheumatoid arthritis. It appears that NSAIDs in-

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duce the apoptosis of synovial cells, by preventing synovial hyperplasia and pannus formation [31].

7. Conclusion

PPAR-γ has been under thorough investigation for over a decade. There has been a marked increase in available data on their involvement in mammalian development, their applications in cardiology, endocrinology and bone metabolism. Even though there have been numerous studies using human and animal specimens the clinical significance of PPAR-γ remains unclear. Not all of its pathways are identified and the PPAR-γ independent actions of its ligands haven't been completely dissociated. Despite these problems, it is a fact that the use of PPAR-γ ligands could be promising for the treatment of arthritis and joint inflammation in general on the premise that its physiology is integrally understood.

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Τα PPAR-γ αποτελούν μέλη μιας οικογένειας υποδοχέων που βρίσκονται σε διάφορα όργανα του σώματος. Η συσχέτισή τους με διάφορα βιοχημικά μονοπάτια να καθιστά για την εύρυθμη λειτουργεία πολλών συστημάτων μεταξύ των οποίων και του μυοσκελετικού. Εκτός από την ήδη καλά μελετημένη δράση τους στην λιπογένεση, τη διαφοροποίηση λιποκυττάρων και την ομοιοστασία της γλυκόζης, φαίνεται να συσχετίζεται με αντιφλεγμονώδη δράση, κυτταρική διαφοροποίηση και απόπτωση. Την τελευταία δεκαετία πραγματοποιείται σημαντική έρευνα για το ρόλο τους στον οστικό μεταβολισμό και την αντιμετώπιση διαφόρων μορφών αρθρίτιδας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: αρθρίτιδα, αρθρικός χόνδρος, PPARs, παθογενετικοί μηχανισμοί