Mutation Research 690 (2010) 57–63

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Role of PPAR-gamma in inflammation. Prospects for therapeutic intervention by food components☆

Harry Martin*

The New Zealand Institute for Plant & Food Research Limited, Palmerston North 4474, New Zealand

ARTICLE INFO

Article history:

Keywords:
Peroxisome proliferator activated receptor gamma (PPARγ)
Inflammatory disease
Diet

ABSTRACT

Peroxisome proliferator activated receptor gamma (PPARγ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. Acting as sensors of hormones, vitamins, endogenous metabolites and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes. PPARγ has been known for some time to regulate adipocyte differentiation, fatty acid storage and glucose metabolism, and is a target of anti-diabetic drugs. More recently, PPARγ has been recognized as playing a fundamentally important role in the immune response through its ability to inhibit the expression of inflammatory cytokines and to direct the differentiation of immune cells towards anti-inflammatory phenotypes. A feature of PPARγ is the structural diversity of its ligands, which encompass endogenous metabolites, dietary compounds and synthetic drugs. The high and increasing incidence of inflammatory and allergic disease, coupled with encouraging results from recent clinical trials, suggest that natural PPARγ agonists found in foods may be beneficial to human health by acting as anti-inflammatory molecules. PPARγ is therefore not only a target of the pharmaceutical industry, but also of great potential interest to the food industry, since it is activated by several natural dietary constituents. The prospects for dietary intervention in inflammatory disease have improved somewhat over the last few years, and are reviewed here.

1. Introduction—PPARγ and its role in inflammation

Inflammatory disease is a broad term encompassing a wide range of pathological conditions affecting many organs and tissues. Inflammatory diseases include inflammatory bowel disease, atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma and psoriasis. The incidence of atopic illness including asthma has increased considerably over recent decades [1]. Ulcerative Colitis and the less prevalent, but more severe, Crohn's disease, were both considered to be the diseases of Western societies but the incidence and prevalence of these illnesses in Asia are increasing [2–4]. The risk of developing colorectal carcinoma is increased for individuals with inflammatory bowel disease [5]. In geographical regions where diets are high in n-3 polyunsaturated fatty acids (PUFAs) cancer incidence is low [6]. It has been suggested that some of the protective effect of dietary n-3 PUFAs may be due to their anti-inflammatory, PPARγ activating properties [7].

The peroxisome proliferator activated receptors (PPARs) are a subset of the nuclear receptor superfamily. Unlike the classical hormone-activated receptors such as the estrogen receptor, which is located in the cytoplasm and translocates to the nucleus after binding of the activating ligand, the PPAR receptors reside in the nucleus bound to DNA response elements [8]. The nuclear location of the PPAR receptor is typical of metabolite-activated nuclear receptors. There are three forms of PPAR receptor: alpha, beta/delta and gamma [9], all of which form obligate heterodimers with the retinoid-X-receptor (RXR-receptor). PPARα is the target for hypolipidaemic drugs known as fibrates. PPARβ/δ is now emerging as an important regulator of bowel cell proliferation/differentiation. The tissue expression of the three PPAR forms is different but overlapping. The functions of PPARγ and PPARα also overlap somewhat. PPARγ is expressed in a range of tissues including adipocytes, skeletal muscle cells, osteoclasts, osteoblasts and several immune-type cells. Unsurprisingly, germ-line knockout of

DOI of original article:10.1016/j.mrfmmm.2009.06.009.

Abbreviations: 15d-PGJ_2, 15-deoxy-Δ12,14 prostaglandin J2; 5-ASA, 5-aminosalicylic acid; c9, t11, cis-9 trans-11; CLA, conjugated linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IgA, immunoglobulin A; IL, interleukin; PPARγ, peroxisome proliferator activated receptor gamma; PUFA, polyunsaturated fatty acid; t10, c12, trans-10, cis-12; TNF-α, tumour necrosis factor alpha.

☆ An error resulted in this article appearing in a previous volume of this journal. The article is reprinted here for the reader's convenience and for the continuity of this special issue. The details of the original publication are as follows [Martin, 2009. Role of PPAR-gamma in inflammation. Prospects for therapeutic intervention by food components. Mutation Research 669, 1–7. 10.1016/j.mrfmmm.2009.06.009].

* Tel.: +64 6 953 7747; fax: +64 6 953 7701.
E-mail address: hmartin@hortresearch.co.nz.

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doi:10.1016/j.mrfmmm.2009.09.009

PPARγ is lethal. Four transcripts of the PPARγ gene are found in human tissue as a result of tissue specific variations in promoters and splicing [10–12]. However in normal cells only two proteins, PPARG-1 and PPARG-2 are expressed. PPARG-1 protein can be produced from transcripts PPARG-1, PPARG-3 and PPARG-4. PPARG-1 protein is widely expressed whereas PPARG-2 is mainly restricted to adipocytes [13].

PPARγ is activated, not only by ligand (agonist) binding, but also by phosphorylation, which increases the ligand-independent transcriptional activity [14]. Apart from its role as a transcription factor, PPARγ also acts as a trans-repressor of macrophage inflammatory genes [15]. In this mechanism the ligand-dependent sumoylation of PPARγ represses inflammatory gene expression. Binding of sumoylated PPARγ to a DNA-bound repressor complex blocks the expression of inflammatory gene products by preventing the 19S proteasome-mediated degradation of the repressor complex. Ligand-independent activation of PPARβ/δ can suppress bowel disease by down regulation of inflammatory signalling [16].

Evidence of the role of PPARγ in inflammatory disease is apparent from genetic screening of patients suffering from multiple sclerosis (MS), an autoimmune disease of the central nervous system. Various genetic linkages to immune genes have been recognized for MS, notably the receptors for interleukin (IL) 2 and IL7. Very recently a PPARγ polymorphism has been added to the list of MS-linked genes. In a study of 116 patients and 211 healthy age-matched controls, the Ala/Ala genotype of the PPARγ Pro12Ala polymorphism was associated with a 10-year, statistically significantly delayed onset of disease in patients with MS [17]. The anti-inflammatory effects of the Pro12Ala polymorphism are corroborated by a recent study of atherosclerosis, a chronic, macrophage-mediated, inflammatory disease of the arterial blood vessels. This 10-year follow-up study of men with coronary artery disease showed that carriers of the Pro12Ala allele of PPARγ have less widespread atherosclerosis and are considerably protected against 10-year vascular morbidity and mortality [18].

The use of PPARγ knockout mice has provided strong evidence for the role of natural PPARγ ligands in controlling inflammation. In a seminal study, colitis was induced in mice deficient in colonic PPARγ by two unrelated mechanisms, either by treatment with oral dextran sodium sulfate or by transfer of $CD4^{+}CD45RB^{hi}$ T-cells. In the former approach colitis is induced by chemical irritation of the mucosa and is dependent on macrophage activation and epithelial cell apoptosis whereas in the latter method, colitis is mediated by antigen driven TH1-cell activation. In both of these models, wild type mice responded to dietary conjugated linoleic acid (CLA) by clinical amelioration of colitis while the colonic PPARγ knockout mice were unresponsive [19].

The anti-inflammatory effects of PPARγ are closely linked with its anti-diabetic effects. Mice with a macrophage-specific deletion of PPARγ were tested for their ability to resist a challenge with *Leishmania major*, a parasitic infection which requires an M1 (cell-mediated) type response from the host for immunity to occur. Mice lacking macrophage PPARγ were not only less susceptible to *Leishmania* spp. infection, as expected, but the same animals were also prone to diabetic illness [20]. Selective knockout of macrophage PPARγ resulted in a reduced capacity for skeletal muscle to metabolise fatty acids and sugars. The expression of transcription factors and co-activator proteins necessary for mitochondrial biogenesis were also greatly reduced. Thus macrophage PPARγ activation not only induces differentiation of macrophages into the non-inflammatory, M2 type but also has profound effects on the metabolic status of the whole mouse.

A similar demonstration of the profound physiological effect of selective knockout (KO) of the PPARγ gene, this time selectively removing the gene from endothelial cells, resulted in the whole-trunk hair loss in the offspring of the KO mice. The mechanism underlying these bizarre symptoms was traced to the default synthesis of toxic, highly inflammatory oxidised lipids in the milk of mice lacking the endothelial PPARγ gene. These oxidised lipids were generated due to a huge excess of lipoxygenase activity, normally repressed by the endothelial PPARγ gene. Accumulation of the inflammatory lipid mediators in the skin of the suckling mice caused inflammation and subsequent alopecia. Skin inflammation was confirmed as the cause of alopecia when topical aspirin cured the inflammation and prevented the hair loss [21]. These examples suggest that systemic inflammation is the default physiological condition, held in check by PPARγ under normal circumstances.

Animal studies and human trials of PPARγ activating drugs, normally used to treat diabetes, have shown these compounds to have great potential as anti-inflammatory drugs. In a mouse model of asthma, pioglitazone, a PPARγ activator, was found to be as effective as dexamethasone, a corticosteroid commonly used in asthma treatment [22]. In a rat model of rheumatoid arthritis known as adjuvant induced arthritis, the PPARγ activating drugs pioglitazone and rosiglitazone, were found to reduce bone erosion and inflammatory bone loss [23]. Using Type II diabetic rats as a model of inflammatory renal disease, pioglitazone reduced nephropathy by an anti-inflammatory mechanism [24]. The successes of PPARγ activators in animal models of the autoimmune disease multiple sclerosis (MS) have given strong support to the use of PPARγ agonists in human trials [25]. The use of rosiglitazone in human inflammatory bowel disease gave beneficial results in an Ulcerative Colitis clinical trial [26]. The US National Institutes of Health are currently recruiting participants for a trial of pioglitazone in the inflammatory diseases rheumatoid arthritis and atherosclerosis (clinical trial identifier NCT00554853). A trial of pioglitazone in asthma (clinical trial identifier NCT00787644) is currently in the planning phase.

PPARγ is of particular interest to the food industry because PPARγ activators and their precursors e.g. linolenic and linoleic acid are abundant in several foods. In addition, certain isoforms of linoleic acid, notably the trans-10, cis-12 isoform are normally rare in the diet but present in higher concentration in certain synthetic food supplements used for weight loss [27]. The t10, c12 isoform of CLA is effective at inducing weight loss in mice, but it does this by antagonising PPARγ and inducing the stress response in adipocytes [28,29]. On the other hand, the cis-9, trans-11 isoform of linoleic acid, which is commonly found in natural food products, inhibits allergic airway sensitization and inflammation in mice [30] via a PPARγ dependent mechanism. The mechanisms by which dietary PPARγ activators may ameliorate inflammatory disease are discussed.

2. Anti-inflammatory effects of PPARγ ligands—synthetic and natural

PPARγ ligands can be divided into various categories: natural/synthetic, endogenous/exogenous or covalent/reversible. To demonstrate the variety of PPARγ ligands, the structures of the ligands discussed in this article are shown in Fig. 1.

PPARγ agonists known as thiazolidinediones are commonly prescribed for the treatment of diabetes but have been investigated for their anti-inflammatory effects. PPARγ protein was identified in the antigen presenting cells, monocytes and macrophages and synthetic PPARγ agonists including pioglitazone, troglitazone and rosiglitazone were shown to suppress production of inflammatory cytokines by these cells [31,32]. Subsequently, PPARγ was identified in dendritic cells which are potent and highly differentiated, professional antigen presenting cells. The same thiazolidinedione compounds were demonstrated to decrease dendritic cell secretion of IL12, a potent TH1-type inflammatory cytokine [33,34].