

PPAR γ and inflammatory bowel disease: a new therapeutic target for ulcerative colitis and Crohn's disease

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Peroxisome proliferator-activated receptor γ (PPAR γ) is a nuclear receptor that is known to play a central role in adipocyte differentiation and insulin sensitivity. Through work in several animal models of intestinal inflammation, it is now recognized that PPAR γ also inhibits tissue injury associated with immune activation. These studies point to PPAR γ as a novel anti-inflammatory mediator with broad therapeutic potential.

The inflammatory bowel diseases (IBD) ulcerative colitis and Crohn's disease are chronic, relapsing enteropathies. Although the definitive etiology of these diseases remains unknown, current theories suggest that a dysregulated mucosal immune response to an unidentified component of normal intestinal microbiota in a genetically susceptible host is at the core of these diseases¹⁻³. In addition to providing a unifying hypothesis to direct experimentation in these diseases, insights into IBD pathogenesis are now driving the development of newer therapeutic interventions beyond the traditional therapies used for the past 25 years, which include 5-aminosalicylates, corticosteroids, antibiotics and immunosuppressants. In this regard, a recent article by Desreumaux and colleagues describes the effectiveness of peroxisome proliferator-activated receptor γ (PPAR γ) and retinoid X receptor (RXR) ligands for the amelioration of colitis in an experimental mouse model⁴. This and other recent articles highlight a new potential direction for the clinical therapy of IBD.

PPAR γ is one of the nuclear receptors that play a central role in adipocyte differentiation and insulin sensitivity⁵⁻⁸. Although the endogenous ligand for PPAR γ remains unclear, 15-deoxy- $\Delta^{12,14}$ -

prostaglandin J₂ and thiazolidinedione derivatives are known to activate PPAR γ . Thiazolidinedione derivatives, such as troglitazone, pioglitazone and rosiglitazone are clinically useful in the therapy of non-insulin dependent diabetes mellitus⁵⁻⁸. Recently, other physiological roles of PPAR γ have been investigated. As the expression levels of PPAR γ in colon and small intestine

of humans and rodents are higher than those observed in other organs⁹⁻¹¹, it is not surprising that an early focus of PPAR γ in the gastrointestinal tract was the role of PPAR γ activation in colon cancer^{10,12-14}. However, it currently remains uncertain whether PPAR γ functions as a suppressor or promotor in these diseases.

PPAR γ in inflammation

More definitive, however, has been the work on the role of PPAR γ in intestinal inflammation. Su and colleagues¹⁵ reported that two thiazolidinedione-derived PPAR γ ligands, troglitazone and rosiglitazone, could inhibit the colonic inflammation associated with dextran sodium sulfate (DSS) administration in mice. The authors also indicated a possible mechanism for the role of PPAR γ in inhibiting colitis: inhibition of nuclear factor κ B (NF- κ B) activation by PPAR γ . Despite the interest that this report generated, several questions remained, as only exogenously administered PPAR γ ligands were used in this study. Moreover, only disease-activity measurements were used rather than other objective indices of colitis. Would it be possible to prove that activation of PPAR γ has anti-inflammatory action using other objective indices of inflammation associated with colitis? Does endogenous PPAR γ play an anti-inflammatory role in physiological conditions? Are the levels of PPAR γ protein in IBD patients lower than those observed in healthy controls, allowing for increased susceptibility of the former to chronic inflammation? These and other questions have been subsequently addressed.

Animal models

Work from our laboratory recently examined PPAR γ ligands and PPAR γ -deficient mice in intestinal inflammation associated with ischemia-reperfusion to clarify the anti-inflammatory role of endogenous PPAR γ . In this report¹⁶, we showed not only the inhibition of inflammation by

PPAR γ ligands, but also the aggravation of injury in the context of PPAR γ deficiency. This report clearly showed that PPAR γ functions as an endogenous anti-inflammatory substance in the intestine and probably in other tissues such as the lung, as remote injury was also affected in this model¹⁶. Thus, PPAR γ might play a role as an anti-inflammatory brake such that a decrease in PPAR γ levels might cause the development or exacerbation of inflammation. Low levels of PPAR γ might exist within the mucosa of IBD patients, which might predispose to unrestrained inflammation as observed in PPAR γ -deficient mice¹⁷. Thus, either decreases in the endogenous ligand(s) for PPAR γ , which remain to be identified, or decrease(s) in the levels of PPAR γ itself might be associated with IBD.

More recently, Desreumaux and colleagues reported the effects of both PPAR γ and RXR ligands in the treatment of experimental colitis using the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis model. They showed important therapeutic contributions of ligands for both molecules. Notably, PPAR γ forms heterodimers with RXR such that several biological effects of PPAR γ activation can be partially reproduced by specific RXR agonists or retinoids. Using mice with heterozygous deficiency of PPAR γ or RXR α , Desreumaux and colleagues also clarified the endogenous roles of both receptors. Both the PPAR γ -deficient (+/-) mice and RXR α -deficient (+/-) mice exhibited an aggravation in inflammation in the TNBS model in comparison with wild-type mice. The results obtained with the PPAR γ - and RXR α -deficient mice support the observations on the effectiveness of combination therapy. Thus, taken together with the reports of Su *et al.* and Nakajima *et al.*, PPAR γ ligands are effective in three different models of colitis: DSS-, ischemia-, and TNBS-induced colitis^{4,15,16}.

Based upon these reports (see Table 1), there is no doubt that endogenous PPAR γ pathways play a

Table 1. Effects of PPAR γ ligands and receptor-deficient mice in inflammatory colitis models

Models	Ligands	Animals	Ref.
DSS-induced	Troglitazone, rosiglitazone		15
Ischemia-induced	Rosiglitazone	PPAR γ (+/-)	16
TNBS-induced	Troglitazone, rosiglitazone	PPAR γ (+/-) RXR α (+/-)	4

^aAbbreviations: DSS, dextran sodium sulfate; PPAR γ , peroxisome proliferator-activated receptor γ ; RXR, retinoid X receptor; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

central role in anti-inflammatory responses in the small intestine and colon. Although several reports have suggested that the anti-inflammatory effects of prostaglandin J₂ and thiazolidinedione derivatives could occur independently of PPAR γ (Refs 18,19), the results obtained with PPAR γ -deficient mice clearly indicate the important anti-inflammatory role of the PPAR γ pathway in the gastrointestinal tract.

Mechanisms of inflammation inhibition

What are the mechanisms by which PPAR γ inhibits inflammation? Although Su *et al.*¹⁵ and Nakajima *et al.*¹⁶ supported the inhibition of NF- κ B as the major mechanism, Desreumaux *et al.* suggested the possibility that PPAR γ also inhibits the Jun N-terminal kinase (JNK) and p38 MAP kinase pathways⁴. These possible mechanisms described by Desreumaux *et al.* are very interesting. Many cytokines, adhesion molecules and other inflammatory mediators are

regulated by NF- κ B (Refs 20–22). In addition, a network of interactions exists between the NF- κ B and MAP kinase pathways as summarized in Fig. 1^{23,24}. It can be suggested, therefore, that such inflammatory networks play an important role in the initiation and progression of inflammation. Future investigations are clearly required to clarify these and other potential anti-inflammatory mechanisms associated with PPAR γ .

New therapeutic strategies for Crohn's disease, such as anti-tumor necrosis factor (TNF)- α therapy, are rapidly emerging from investigations into the basic pathogenesis of IBD (Refs 25,26). The studies outlined above support PPAR γ as a novel and potentially fruitful target for therapies directed at ulcerative colitis and Crohn's disease. Indeed, clinical trials are now underway in several institutes with interesting preliminary data²⁷. These early clinical observations in conjunction with *in vivo* animal models warrant further investigation into the

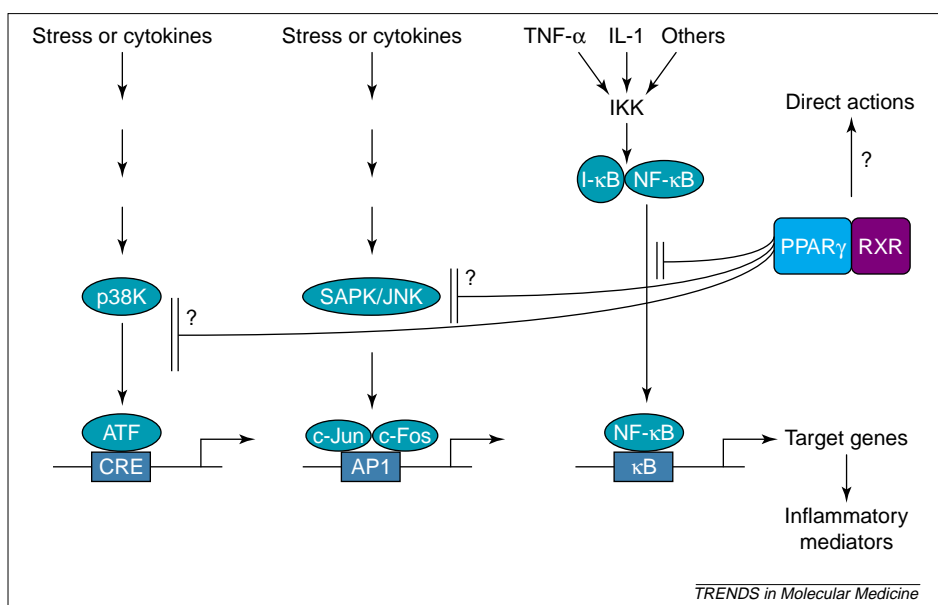


Fig. 1. Possible mechanisms of anti-inflammatory effects of PPAR γ -associated pathways. Abbreviations: AP1, activator protein 1; CRE, cAMP response element; I- κ B, inhibitor of NF- κ B; JNK, Jun N-terminal kinase; IL, interleukin; NF- κ B, nuclear factor κ B; TNF- α , tumor necrosis factor- α .

immunobiology of PPAR γ and its potential role as a therapeutic target in intestinal inflammation.

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Meeting Report

The PPARs 2001: it's not over 'til the fat lady sings

Barry Marc Forman

Recent advances into peroxisome proliferator-activated receptors (PPARs) were presented at a Keystone Symposium entitled 'The PPARs 2001: A Transcription Odyssey', in Keystone, CO, USA, 4–10 February, 2001.

The peroxisome proliferator-activated receptors (PPARs) α , γ and δ are nuclear receptors for endogenous lipids¹. These receptors have been linked to a variety of common diseases, and synthetic PPAR γ ligands (thiazolidinediones, TZDs) are now being used to treat type 2 diabetes. Given that these receptors were virtually unheard of ten years ago, it is probably safe to say that growth of the PPAR field has rivaled that of the dot com industry.

Novel PPAR ligands

PPARs act as receptors for fatty acids and their metabolites. For example, 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-J₂) binds to PPAR γ and induces adipocyte differentiation in a PPAR γ -dependent fashion. Although 15d-J₂ can activate PPAR γ , it is less clear whether it is the endogenous ligand in all PPAR γ -expressing cells and tissues (e.g. fat, macrophages and intestinal epithelia). Additional or alternative ligands might exist and their identification is crucial as they will ultimately control PPAR action *in vivo*.

A report from T. McIntyre (Salt Lake City, UT, USA) provided the first evidence that an oxidized phospholipid (hexadecyl azelaoyl phosphatidylcholine) can serve as a high-affinity ligand ($K_d \sim 50$ nM) for



PPAR γ . Previously identified ligands are less complex fatty acids with 10–100 times lower affinities. These results raise the possibility that oxidized phospholipids might serve as a direct link between cholesterol homeostasis and PPAR γ (see below). However, as this new ligand is generated by oxidative stress, it might not represent a physiological ligand.

PPARs and cholesterol homeostasis

Although initial clinical studies suggested that TZDs might inhibit atherogenesis, a subsequent report demonstrated that PPAR γ induces expression of CD36, a scavenger receptor responsible for internalization of cholesteryl esters and fatty acids. Moreover, *in vitro* exposure of macrophages to 15d-J₂ induced the formation of foam cells, the major cellular components of the fatty streak. This implies that PPAR γ could contribute to atherogenesis, an interpretation that is limited by the fact that 15d-J₂ has PPAR γ -independent effects². Thus, the PPAR γ -cholesterol connection was a hot

topic at this meeting as there is potential concern for the millions of diabetics currently being treated with PPAR γ agonists.

The overall role of PPAR γ in cholesterol homeostasis might have been put to rest by C. Glass (San Diego, CA, USA) who reported that TZDs inhibit atherogenesis in a rodent model of hypercholesterolemia³. A flurry of molecular studies from several labs helps explain how this occurs. First, PPAR γ activates CD36 in tissues other than macrophages (e.g. fat), thereby shifting the distribution of lipids to these other tissues. Second, PPAR γ activates expression of another nuclear receptor, LXR α , which in turn enhances macrophage cholesterol efflux by stimulating expression of the ABCA1 export pump.

Additional mechanisms underlying the anti-atherogenic effects of PPAR γ were presented by members of Glass' lab using a clever assay to monitor monocyte entry into atherosclerotic lesions. The results indicate that PPAR γ agonists inhibit monocyte recruitment and decrease lipid accumulation in these lesions. But are these effects autonomous for the monocyte-derived cells, or do they represent the net physiological effects of PPAR γ activation in multiple tissues? R. Evans (San Diego, CA, USA) addressed this question by performing bone-marrow transfer from PPAR $\gamma^{-/-}$ donor mice to hypercholesterolemic recipients. Atherosclerosis worsened in the recipients suggesting that