Role of Peroxisome Proliferator Activated Receptor-gamma and its Ligands in Inflammatory Bowel Disease

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ABSTRACT

Peroxisome proliferator-activated receptor-gamma (PPAR-γ), a nuclear receptor, is highly expressed in the colonic epithelium in contrast to its impaired expression in the patients with ulcerative colitis (UC). Several natural and synthetic ligands of PPAR-γ with some effects in the colon have been identified. The aim of this review is to provide an overview of the role of PPAR-γ and its ligands in inflammatory bowel disease (IBD). Review of article was done using a PubMed search. Animal model studies have revealed that PPAR-γ is the key receptor for 5-aminosalicylic acid that mediates its main effects in the colon. Moreover, the clinical trials have shown that the PPAR-γ agonist rosiglitazone is effective in the treatment of mild to moderately active UC. PPAR-γ gene therapy, used as an adjunct intervention, may be effective in suppressing inflammation in colitis. Some commensal bacteria and natural ligands present in food may induce PPAR-γ expression and activation in the colon which suggest the possibility of associating a natural regulator and a synthetic ligand of PPAR-γ as drug therapy for IBD patients. Further studies are required for the development of unique and effective therapies with PPAR-γ agonists in IBD patients.

INTRODUCTION

Current advances suggest that an inappropriate response of a defective mucosal immune system to the indigenous intestinal flora and other luminal antigens in a genetically susceptible host is at the core of the pathophysiology of inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD).[1,2] Because of the regulatory action in the colon and involvement in immune response, peroxisome proliferator-activated receptor-gamma (PPAR-γ) has become a hot research topic in gastroenterology. After a brief description of PPAR-γ, this review aims to provide an overview of the role of PPAR-γ with the latest findings about the use of its ligands in IBD. A computerised medical literature search of all English language articles was done from the "PubMed" online database with the keywords "peroxisome proliferator activated receptor-gamma", "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "colitis", "PPAR gamma ligands" and "rosiglitazone".

PPAR-γ structure and its expression in different tissues including colon

The peroxisome proliferator-activated receptors (PPAR) are nuclear receptors, which are intracellular transcription factors that regulate the activity of complex gene networks.[3] The PPAR subfamily of nuclear hormone receptors include distinct genes that code for several PPAR isoforms denoted: PPARα, β/δ and γ.[4] The human PPAR-γ gene is composed of nine exons spanning more than 100 kb of genomic DNA5 on chromosome 3p25 in the proximity of the locus for the retinoic acid receptor RAR-β (3p24) and the thyroid receptor TR-β (3p21).[6,7] The PPAR-γ was initially identified for its role in adipocyte differentiation and regulation of genes involved in lipid and glucose metabolism. However, activation of PPAR-γ also can antagonize nuclear factor κB (NFκB) action in macrophages resulting in downregulation of proinflammatory cytokines.[8-15]

The expression of PPAR-γ is found not only in adipocytes but also in a number of other cells types, such as macrophages, lymphocytes, hepatocytes, and skeletal muscle.[16] Very high expression levels of PPAR-γ are also found in the colonic epithelium.[17] In both rodents and humans, the level of receptor in colon tissue is equal to, or greater than, that in adipose tissue. In addition, studies have reported higher expression levels of PPAR-γ in the distal colon than in the proximal colon and small intestine.[18] Moreover, PPAR-γ expression is primarily localized in the more differentiated epithelial cells of the colon.[19,20] The localization in differentiated cells is consistent with the numerous reports of PPAR-γ induction upon differentiation of cultured colon cells.[19, 21-23] Thus, the expression and activation of PPAR-γ are associated with a differentiated phenotype in intestinal cells.

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The expression of PPAR-γ by epithelial cells could be regulated by bacteria, which might explain the characteristic and important PPAR-γ pattern expression in the colon compared with other parts of the digestive tract.[24] It is noteworthy to mention that lipopolysaccharide (LPS) of Gram negative bacteria seems to be critical in colonic steady state PPAR-γ expression through Toll-like receptor (TLR)-4.[24]

IMPACT OF MUTATIONS IN PPAR-γ GENE

The polymorphism in the PPAR-γ2 gene (Pro12Ala), which is a CCA-to-GCA missense mutation in codon 12 of exon B of the PPARγ gene, was recently identified.[25] This substitution possibly results in a conformational change in protein structure and reduced function of the PPARγ gene. At the cellular level, reduced binding of the Ala variant to the PPARγ-responsive DNA elements and reduced transcription of specific genes in cells overexpressing the Ala variant have been reported.[26,27] The Ala allele of the common Pro12Ala polymorphism is associated with a reduced risk of type 2 diabetes.[28] This polymorphism also appears to have a protective effect against diabetic nephropathy.[29] Individuals with the Ala allele are also found to have a reduced risk of colorectal cancer.[30-32] Another single nucleotide polymorphism (SNP) in the PPAR-γ gene (C161T) is a silent C to T substitution in nucleotide 161 of exon 6 and does not cause an amino acid change.[33] The C161T polymorphism has been correlated with the colorectal cancer,[34] colorectal adenoma[35] and with other conditions such as psoriatic arthritis,[36] diabetic nephropathy,[37] plasma leptin levels in obese subjects,[33] extent of coronary artery disease by angiography,[38] carotid intima media thickness,[60] and incidence of myocardial infarction among individuals younger than age.[29]

Association of PPAR gamma polymorphism with IBD

Different studies have shown the variable results about the association of polymorphism of PPAR-γ with IBD. The significant association between PPAR-γ polymorphisms and the development of CD and UC at single loci level and also in haplotype combinations, was shown in a Hungarian study, suggesting a potential protective effect of the Ala allele in IBD.[39] In the study done in Chinese population, the potential association was found between the PPAR-γ C161T polymorphism and UC patients, but the finding was not replicated in the Dutch population.[40] In one recent Danish study, a statistically significant (although modest) association was determined between the homozygous PPAR-γ Pro12Ala variant genotype and an increased risk of IBD.[41] However, in one study from Japan, Plo12Ala polymorphism of PPAR-γ was not found to be associated with the risk of developing UC.[42] Similarly, another study from Turkey also showed that Pro12Ala polymorphism in the PPAR-γ gene was not related to the risk of the development of inflammatory bowel disease.[43] The inconsistent results of different studies demand for the more studies with larger representative samples of IBD to find the concrete data about the polymorphism of PPAR-γ in IBD patients.

ROLE OF PPAR-γ IN IBD

The strongest evidence for an anti-inflammatory role of PPAR-γ comes from the studies which indicated that heterozygous PPAR-γ deficient mice were more susceptible to dextran sodium sulphate (DSS) and 2,4,6-trinitrobenzene sulfonic acid (TNBS) induced colitis.[44] DSS induced colitis, in particular, is an acute inflammation model primarily driven by epithelial disruption and macrophage infiltration. The data indicates that PPAR-γ expression in certain cell types of the colon plays an anti-inflammatory role. Recent studies elaborated on these findings by showing that mice deficient in PPAR-γ expression in epithelial cells and macrophages displayed increased pro-inflammatory gene expression and susceptibility to DSS colitis.[45,46] These findings suggest that PPAR-γ expression in at least two cell types, epithelial and macrophage, can protect against at least one model of acute colitis (DSS). Experimental models of colitis can also be initiated by distinct mechanisms and driven by infiltration of different cell types, both epithelial and immune cells.[47-49] However, the importance of tissue specific PPAR-γ expression may depend largely on the model of colitis examined, emphasizing the need to utilize multiple models to accurately represent manifestations of human colitis. Despite evidence for anti-inflammatory actions of the RXR/ PPAR-γ heterodimer in the colon in animal models, the role of PPAR-γ in IBD in humans is little explored.

The study done in the UC patients showed an impaired expression of PPAR-γ at the mRNA and protein levels.[50] This study also revealed the comparable levels of PPAR-γ in peripheral mononuclear cells of IBD patients and controls and absence of specific mutations of the PPAR-γ gene or its promoter in UC patients which suggest that epigenetic events may account for impaired PPAR-γ expression in UC patients.[50]

The study was done to test the relationship between PPAR-γ alleles and CD in humans, which was based on SAMP1/YitFc animal findings developing spontaneous ileitis due to a defect in expression of PPAR-γ in ileal crypts, secondary to inheritance of AKR alleles in the region of PPAR-γ.[51] The study showed that two intronic polymorphisms SNP1($p<10^{-5}$) and SNP2($p\leq10^{-3}$) exhibited lower allele frequencies in 134 CD patients compared with 125 controls.[51]

PPAR-γ LIGANDS IN IBD

Natural PPAR-γ ligands

Naturally occurring substances such as polyunsaturated fatty acids, certain eicosanoids, and 15deoxy-Δ12,14-PGJ2 (15d-PGJ2) have been found to be the weak activators of PPAR-γ.[52] They have intrinsically low binding affinities and weak in vivo concentrations in intestinal cells; hence, many of these compounds do not support physiological functions. The minimal concentrations of 15d-PGJ2 required to activate PPAR-γ are approximately 10–150-fold higher that those found in human intestinal epithelial cells.[53] Studies have shown that conjugated linoleic acids protected mice from experimental colitis by the activation of PPAR-γ.[54] This effect was not seen in mice with colonic knockout of PPAR-γ. Since the food derived bacterial metabolites are the main source of linoleic acids in the gut, the food supplements might have positive effect on intestinal inflammation mediated via PPAR-γ.[55] This PPAR-γ could play an important role in the homeostasis of intestinal microflora and the epithelial barrier. In normal mucosa, PPAR-γ in intestinal epithelial cells could recognize luminal bacterial metabolites and then set the threshold of NFkB activity as one of the most important proinflammatory transcription factors. The unsaturated fatty acid derivative nitrolinoleic acid (LNO2), generated via nitric oxide dependent oxidative inflammatory reactions, has been identified as a

new PPAR-γ agonist.[56] Present in the vascular cell wall as the most abundant bioactive oxide of nitrogen and in the blood of healthy individuals at concentrations of approximately 500 nM, LNO2 is considered at present to be one of the most potent physiological endogenous natural ligand of PPAR-γ.[57] Further studies are needed to determine intestinal effects of LNO2 in the maintenance of gut homeostasis and during inflammatory disorders.

Synthetic PPAR-*y* ligands

Thiazolidinediones (TZDs), such as trogliazone, rosiglitazone and pioglitazone, are high affinity synthetic ligands of PPAR-γ, frequently referred to as "PPAR-γ agonists".[58] TZDs are currently used as insulin sensitizing agents in the treatment of type 2 diabetes mellitus.[57] Glitazar is a novel family of dual acting PPAR-α/γ agonist developed as an oral treatment for insulin resistance related glucose and lipid abnormalities associated with type 2 diabetes and the metabolic syndrome.[59] Non-steroidal anti-inflammatory drugs are also reported in vitro as PPAR-γ ligands but in vivo their binding affinities of 0.1 mM are 1000-fold higher than the mean concentrations found in patients conventionally treated with these drugs.[60]

5-Aminosalicylic acid (5-ASA) is an anti-inflammatory drug widely used in the treatment of IBD. It is known to inhibit the production of cytokines and inflammatory mediators, but the mechanism underlying the intestinal effects of 5-ASA remained unknown. The study showed that PPAR-γ is the key receptor for 5-ASA that mediates its main effects in the colon.[61] A small-sample open- label study showed that the patients with mild to moderately active UC refractory to the standard therapies may benefit from therapy with PPAR ligands.[62] Another study showed that the combined treatment with rosiglitazone and 5-ASA had better therapeutic effect than 5-ASA alone in mild to moderately active UC.[63] Encouraging results were reported in yet another multi-center, randomized, doubleblind, placebo-controlled clinical trial, which showed that rosiglitazone was effective in the treatment of mild to moderately active UC patients.[64] However, there is considerable concern regarding whether the adverse effects of thiazolidinediones would outweigh the potential benefit for patients with UC.

The reports were published referring about the greater risk of myocardial infarction estimated with the last updated myocardial event rates as an odds ratio of 1.29 (95% CI, 1.01–1.66, P = 0.05).[65-67] The cardiovascular adverse events occurred more frequently in subgroups of susceptible patients treated with rosiglitazone for at least 24 weeks,68 having type 2 diabetes, long-term nitrate use, and/or concurrent insulin therapy.[69] The mechanism for the apparent increase in the rosiglitazone-induced myocardial infarction rate remains unknown but is not regarded as a PPAR-γ ligand effect because the other thiazolidinedione pioglitazone widely used to treat type 2 diabetes has significant protective effects on coronary and peripheral vascular events[70]; pioglitazone does not increase the risk for myocardial infarction and may decrease the risk for stroke and revascularization.[71] However, while treating the UC patients with thiazolidinediones, it is better not to use such therapy in patients with concomitant diseases such as liver disease, congestive heart failure, or in those at particularly high risk for myocardial infarction.

PPAR-γ GENE THERAPY IN IBD

In order to enhance the limited therapeutic efficacy of synthetic PPAR-γ ligands in established colitis, the study was done with the PPAR-γ gene therapy as an adjunct intervention and has shown that the gene therapy alone also was effective in suppressing inflammation and attributed this finding to the action of endogenous agonists.[72]

CONCLUSION

Although the current data supports a role for PPAR-γ expression and activation in epithelial and immune cell types in the control of colonic inflammation, given that only few studies are available so far about the PPAR-γ in IBD, more studies are still necessary to confirm the understanding of the mechanism of the anti-inflammatory actions of PPAR-γ, understanding of factors affecting thiazolidinedione efficacy and understanding of the adverse effects of short and long term use of thiazolidinediones in IBD. The recent discovery that some commensal bacteria and natural ligands present in food may induce PPAR-γ expression and activation in the colon suggest about the potential of associating a natural regulator and a synthetic ligand of PPAR-γ as drug therapy for IBD patients. The report of 5-ASA as a new synthetic ligand of PPAR-γ has encouraged the researchers to develop new drugs, similar to 5-ASA but with a more topical effect in the gut, a stronger affinity to PPAR-γ and minimal adverse effects, so that they could be used more effectively in the induction and maintenance treatment of UC in the future. PPAR-γ gene therapy may be a promising adjunct therapy in suppressing the inflammation in the patients of UC. However, more animal and clinical studies of PPAR-γ in IBD are needed for the development of unique and effective therapies for IBD patients.

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