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PPARγ

Significance of anti-inflammatory effects of PPARγ agonists?

G Rogler

Peroxisome proliferator activated receptor γ expression in mucosal epithelial cells seems to be crucial for its anti-inflammatory effects with respect to experimental colitis, and for maintaining homeostasis of the mucosal barrier, at least in animal models

The peroxisome proliferator activated receptor γ (PPARγ) is one of three members of the PPAR family (PPARα and PPARδ), which itself is a part of the nuclear hormone receptor superfamily.[1–5] Nuclear hormone receptors are transcription factors that are activated by the binding of small lipophilic ligands.[6–11] They induce or repress transcription of a large number of different genes thereby influencing cellular functions.

PPARγ was initially identified for its role in adipocyte differentiation and regulation of genes involved in lipid and glucose metabolism.[12–15] However, activation of PPARγ also can antagonise nuclear factor κB (NFκB) action in macrophages resulting in downregulation of proinflammatory cytokines.[10 16–22] Implicated in these anti-inflammatory properties, PPARγ is not only expressed in adipocytes but also in a number of other cells types, such as macrophages,[9] lymphocytes, hepatocytes, and skeletal muscle. Very high expression levels are found in the colonic epithelium.[23]

Interestingly, the proinflammatory genes that are repressed by PPARγ overlap but are not identical to the genes that are downregulated by the glucocorticoid receptor (GR), another member of the nuclear hormone receptor superfamily which intracellularly mediates the effects of endogenous cortisol and therapeutically administrated glucocorticoids.[24] PPARγ mediated effects in the experimental setting of toll-like receptor stimulation were independent of NFκB and interferon regulatory factor, in contrast with GR action.[24] This indicates that glucocorticoids and ligands of PPARγ could have additive therapeutic effects.

The eicosanoids 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid as well as 15deoxy-Δ12, 14,-prostaglandin J2 have been identified as naturally occurring ligands of PPARγ.[3 25] Thiazolidinediones (TZDs) are high affinity synthetic ligands of PPARγ, frequently referred to as "PPARγ agonists".[26] TZDs are currently used as insulin sensitising agents in the treatment of type II diabetes mellitus.[26–28]

Due to the anti-inflammatory properties of PPARγ, the therapeutic efficacy of eicosanoids and TZDs has been evaluated in different models of inflammation.[6 29–34]

PPARγ has gained interest among gastroenterologists[35] as it was consistently demonstrated that PPARγ ligands reduced mucosal damage and prevented or downregulated the inflammatory response in several murine models of intestinal inflammation.[23 36–41] Recently, further evidence of an anti-inflammatory role of the TZD-PPARγ ligand rosiglitazone was found in interleukin (IL)-10 deficient mice in which rosiglitazone delayed the onset of colitis[42] and in trinitrobenezene sulphonic acid induced colitis in rats in which it reduced mucosal ulceration and TNF secretion.[43] Overexpression of PPARγ by an adenoviral construct in mucosal epithelial cells in mice was associated with amelioration of experimental inflammation.[44]

However, TZDs are not the only agents that could become important in terms of the therapeutic use of the effects of PPARγ. Activation of PPARγ by conjugated linoleic acids also protected mice from experimental colitis.[45] This effect was not seen in mice with colonic knockout of PPARγ. As linoleic acids in the gut are mainly food derived bacterial metabolites, this finding raised the possibility of positive effects of food supplements on intestinal inflammation mediated via PPARγ.[46] This linked PPARγ mediated effects with homeostasis of intestinal microflora and the epithelial barrier. In normal mucosa, PPARγ in intestinal epithelial cells could recognise luminal bacterial metabolites

and then set the threshold of NFκB activity as one of the most important proinflammatory transcription factors.

Another aspect of the therapeutic potential of PPARγ agonists is prevention of colitis associated cancer. Ligand activation of PPARγ in colon cancer cells caused a reduction in linear and clonogenic growth.[47] Human colon cancer cells transplanted into mice showed significant reduction of growth when the animals were treated with TZDs.[47] Loss of function mutations in PPARγ have been described as associated with human colon cancer.[48] In different experimental settings, a role for PPARγ in the prevention of colonic carcinoma was confirmed.[38 49] Furthermore, specific colitis associated colon carcinogenesis is suppressed.[50]

Desreumaux *et al* presented evidence that the therapeutic effect of 5-aminosalicylic acid (5-ASA) may be mediated by PPARγ.[51] 5-ASA treatment had beneficial effects on colitis in wild-type mice but not in heterozygous PPARγ knockout animals.[51] In epithelial cells, 5-ASA increased PPARγ expression and promoted its translocation from the cytoplasm to the nucleus where it induced a modification allowing recruitment of cofactors for the regulation of transcription.

In contrast with the high number of studies on PPARγ effects in murine models, data derived from human mucosa or patients with inflammatory bowel disease (IBD) are rare. Little is known of expression of PPARγ in human mucosa, expression of enzymes producing endogenous ligands, or the cell type in which PPARγ expression may be most relevant. However, there are data indicating reduced expression of PPARγ in ulcerative colitis but not in Crohn's disease.[52] A pilot study in patients with active ulcerative colitis refractory to standard medical therapy has shown some beneficial effects of TZDs.[53] Confirmation of these early studies is still lacking.

In recent years, aspects other than the therapeutic potential of PPARγ agonists have been discussed. Contradictory results had been published on the cell type in which PPARγ expression is important or altered during mucosal inflammation. In 2003, Katayama *et al* demonstrated a dramatic reduction in PPARγ expression during dextran sodium sulphate (DSS) induced colitis in lamina propria lymphocytes and macrophages whereas colitis did not alter PPARγ expression in colonic epithelial cells.[44] In contrast, in the same year, Dubuquoy *et al* presented evidence that PPARγ is expressed primarily in mucosal epithelial cells with only low expression in lamina propria macrophages and almost no expression in lymphocytes.[52] Hence additional information on the mechanism of action of PPARγ agonists in the intestinal mucosa and on the cell type in the gut mucosa most relevant for these effects are urgently needed.

In this issue of *Gut*, Adachi and colleagues[54] present an elegant study answering one of these important questions ***(see page 1104)***. They provide evidence that PPARγ expression in mucosal epithelial cells is crucial for its anti-inflammatory effects with respect to colitis.[54] They generated mice with targeted disruption of the PPARγ gene in intestinal epithelial cells using a villin-Cre transgene and floxed PPARγ allele and induced colitis by DSS administration. Disruption of the PPARγ gene was followed by reduced expression of PPARγ target genes such as the fatty acid binding protein in epithelial cells. These mice showed increased susceptibility to DSS induced colitis with increased mRNA expression of proinflammatory cytokines such as IL-6, IL-1β, and tumour necrosis factor. Interestingly, the PPARγ ligand rosiglitazone decreased the severity of experimental colitis and suppressed cytokine production in both PPARγ wild-type mice and mice with epithelial loss of PPARγ in the mucosa ($PPAR^{\Delta IEpC}$ mice). These results indicate that expression of PPARγ in mucosal epithelial cells is indeed crucial for prevention of colitis and for maintaining homeostasis of the mucosal barrier, at least in animal models. However, the data also indicate that there are PPARγ independent pathways by which TZD exert their anti-inflammatory potential during colitis.

So, what progress have we made investigating the role of PPARγ for the treatment of IBD? Are the anti-inflammatory effects of PPARγ agonists significant? We know that PPARγ agonists are effective in the treatment of colitis in animal models. We now know that we have to target epithelial cell PPARγ.[54] We know that there is decreased expression of PPARγ in patients with ulcerative colitis and that the beneficial effect of 5-ASA in the treatment of ulcerative colitis may be mediated (at least in part) by this nuclear receptor. However, all of these facts do not justify treatment of patients with PPARγ in clinical practice. There is an emerging need to unequivocally show the clinical effectiveness of PPARγ agonists in placebo controlled, randomised, multicentre trials. As the recent study of Ogawa *et al* indicates, there may even be synergistic effects of glucocorticoids and PPARγ agonists on the transrepression of TLR responsive genes playing a role in the maintenance of the intestinal barrier,[24] raising the question of whether a clinical trial should contain an arm with a combination of both drugs. The significance of the anti-inflammatory effects of PPARγ agonists in human IBD will be in doubt as long as a good clinical study is still lacking.

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Crohn's disease

Recurrence rates in Crohn's disease: predicting the future and predicting the past

D B Sachar

Phenotypic features at diagnosis of Crohn's disease may help predict subsequent disease flares and operations

> ''A guy ought to be very careful in making predictions, especially about the future.'' [Yogi Berra (1925–), professional baseball player and manager]

The Holy Grail of Crohn's disease—aside from finding the elusive cause and cure—is understanding its ''natural history''; that is, how it develops, presents, evolves, and responds to different therapies. A principal objective of this level of understanding would be the ability to *predict* the course of disease in any given individual or group of individuals. This aim has been the focus of clinical studies of inflammatory bowel disease for nearly four decades.

One of the earliest attempts to find clinical markers to predict outcomes was made by the late FT de Dombal in Leeds, who proposed a rise in serum β-globulin as an early warning sign of impending flare of ulcerative colitis.[1] Later efforts to develop laboratory predictors of Crohn's disease flares included studies by Brignola *et al* in Bologna.[2] A sharper focus on clinical predictors, as distinct from pure laboratory indices, was introduced by JP Wright in Cape Town.[3] All of these studies were as well intentioned as, but not much more successful than, the search for the historical Holy Grail had been over the previous millennium.[4]

Meanwhile, a less sophisticated but perhaps more intuitive approach to forecasting the clinical course of