Review Article

PPARγ in Inflammatory Bowel Disease

Vito Annese, Francesca Rogai, Alessia Settesoldi, and Siro Bagnoli

Gastroenterology Unit, Careggi, University Hospital, 50134 Florence, Italy

Correspondence should be addressed to Vito Annese, annesev@aou-careggi.toscana.it

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Peroxisome proliferator-activated receptor gamma (PPARγ) is member of a family of nuclear receptors that interacts with nuclear proteins acting as coactivators and corepressors. The colon is a major tissue which expresses PPARγ in epithelial cells and, to a lesser degree, in macrophages and lymphocytes and plays a role in the regulation of intestinal inflammation. Indeed, both natural and synthetic PPARγ ligands have beneficial effects in different models of experimental colitis, with possible implication in the therapy of inflammatory bowel disease (IBD). This paper will specifically focus on potential role of PPARγ in the predisposition and physiopathology of IBD and will analyze its possible role in medical therapy.

1. Introduction

The peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor highly expressed in adipose tissue but also intestine, playing a key role in regulation of insulin resistance and inflammation. Recently its role in intestinal diseases, especially colon cancer and intestinal inflammation, is emerging. The discovery that it is the major functional receptor mediating the aminosalicylate activities in inflammatory bowel diseases (IBD) has further enhanced the interest for the role of this receptor in the regulation of gut homeostasis, with possible implication for newer therapeutic targeting. After an extensive search of medical literature in English language from the PubMed database, we aim in this paper to focus on potential role of PPARγ in the predisposition and physiopathology of IBD and to analyze its role in experimental colitis and potential therapy for IBD.

2. IBD and PPARγ: Friend or Foe

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are common causes of gastrointestinal illness characterised by chronic, relapsing intestinal inflammation, often presenting in early childhood [1]. The incidence varies according to geographical location and in Northern Europe IBD may affect up to one in two hundred of the population [2]. The division into CD and UC is made on the basis of clinical, radiological, endoscopic, and histological features. Common clinical features of CD include abdominal pain, diarrhea, weight loss, and fever. Rectal blood loss is not always a feature and up to 10% of patients with CD may not have diarrhea. Inflammatory changes are patchy in distribution and may occur anywhere within the gastrointestinal tract from the mouth to the anus. Approximately 40% of patients with CD will have disease involving both small and large bowel, in 30% the disease is limited to the small bowel, and 27% percent will have colonic disease only. A small minority of patients will have involvement of the more proximal gastrointestinal tract. Inflammation is transmural and histological examination of bowel and lymph nodes will demonstrate epithelioid cell granulomas in 60–70% of cases. In contrast, patients with UC usually present with bloody diarrhea [3]. There may be associated abdominal pain, urgency, and tenesmus. The disease is limited to the mucosal layer of the colon; it will always involve the rectum and may extend proximally in a continuous fashion.

Current knowledge of aetiology is incomplete, but increasing evidence points towards a combination of environmental triggers in a genetically susceptible individual. More specifically, the intestinal inflammation is thought to result from an inappropriate immune response to microbial antigens of commensal microorganisms [4]. Both diseases manifest themselves primarily in the gastrointestinal tract yet
controlled inflammation

Colitis

Figure 1: An hypothetical model of influence of PPARγ expression in ulcerative colitis. Induction of PPARγ expression in epithelial cells by bacterial lipopolysaccharide- (LPS-) activated TLR4, in turn leads to break NFκB and MAPK pathways to produce inflammatory mediators. The reduced expression of PPARγ together with TLR4 upregulation might enhance the inflammatory mediators production thus resulting in mucosal damage.

can, in principle, affect all of the organ systems of the body. IBD is also associated with an increased risk of colorectal cancer, which itself is already the third most common cancer in developed countries [2].

The progress in gene discovery in complex disease genetics has increased rapidly in recent years, boosted by the advent of genomewide association (GWA) studies. Few complex diseases have seen as much rapid progress as CD and UC thanks specially to the international inflammatory bowel disease genetics consortium (IIBDGC) who collected around the world some 20,000 cases for each of CD and UC (http://www.ibdgenetics.org/). The statistical power of such large sample sets has proven highly effective in identifying multiple susceptibility loci, even where these confer only modestly increased risk of disease. To date there are 99 IBD susceptibility loci: 71 associated with Crohn's disease, 47 with ulcerative colitis, and 28 with both CD and UC [5, 6]. Amongst these are multiple genes involved in IL23/Th17 signaling (IL23R, IL12B, JAK2, TYK2, and STAT3), genes involved in autophagy, intracellular bacteria processing and innate immunity (NOD2, IRGM, and ATG16L1), and genes involved in barrier (HNF4A, LAMB1, CDH1, and GNA1e). However, from these studies, included the recently reported data with the immunochip from the IIBDGC at DDW 2012 [7], no striking signal of PPARγ gene polymorphisms is emerged, with P values of tagging SNPs ranging from 0.005 to 0.01 (personal communication). Poliska et al. have investigated the association of four polymorphisms of PPARγ and IBD; they found haplotypes with both protective and increased risk [8]. Other studies, however, lead to conflicting results [9–13]. Accordingly, a meta-analysis of seven studies with over one thousand UC and CD found no significant association of the Pro12 Ala polymorphism of PPARγ with IBD [14].

In contrast, PPARγ is highly expressed in colonic epithelial cells and to a lesser degree into macrophages and lymphocytes [15]. In addition, its expression in the colon is closely linked to intestinal-microbial interaction. Using quantitative PCR, western blot, and immunohistochemical assay, a 60% decreased expression of PPARγ was observed at the mRNA and protein levels in the colon of UC patients, compared with CD and controls [16]. This impaired expression was found in both inflamed and noninflamed areas and limited to epithelial cells, suggesting that this modified expression is not secondary to the inflammatory process (Figure 1). A possible explanation is the occurrence of epigenetic changes [16]; this hypothesis is corroborated by the demonstration of similar levels of PPARγ in peripheral mononuclear cells of IBD patients and controls and lack of significant polymorphisms of PPARγ in UC patients. Another intriguing possibility is that the Toll-like receptor 4 (TLR4) signaling to PPARγ is impaired in UC. The resulting imbalance between elevated levels of TLR4 and reduced expression of PPARγ may lead to loss of mucosal tolerance to luminal LPS, resulting in mucosal inflammation [16]. In contrast, Yamamoto-Furusho et al. reported that the mRNA PPARγ expression was significantly reduced in the mucosa with active UC compared to the mucosa of patients in remission, with a significant correlation with disease activity [17].

More recently, another important role of PPARγ in the modulation of intestinal inflammation has been put forward. In healthy individual, immune cells and gut mucosa remain largely inactive towards 10^{14} bacteria of the intestinal microflora. This tolerance is attributed to the prominent presence of regulatory immune cells that may be triggered by the resident microflora and whose function is antagonistic to inflammatory pathways stimulated by pathogenic bacteria [18]. The effector cells are M1 macrophages and dendritic (De) cells secreting inflammatory mediators including factors stimulating additional resting macrophages, dendritic cells precursors (monocytes), and T cells. De and M1 present
antigen to resting T cells while secreting cytokines (IL12, IFN-γ, TNF-α, and IL-23) and induce the differentiation to proinflammatory T-helper, specifically Th1 and Th17. The immune response kills the invading bacteria, but may also cause indiscriminate tissue damage. In sterile organ systems, the inflammatory process usually ceases once the antigen population is eliminated. However, in the gut because of the resident microflora, the antigen population cannot be eliminated and the mounted inflammation could be more harmful for the host than the invading bacteria itself, for example, increasing gut permeability and infiltration of bacteria in the lamina propria. In healthy individuals, the gut mucosa contains various regulatory factors such as M2 macrophages, tolerogenic dendritic cells (Dt), and T regulatory cells. This regulatory pathway, by binding to ligands recognized as self to specific receptors, induces the differentiation and switches from M1 to M2 and from De to Dt. One such receptor is PPARγ expressed in T cells, dendritic cells, macrophages, and epithelial cells [19, 20].

3. PPARγ: Structure, Function, and Expression in the Gut

PPARγ belongs to the nuclear receptor family consisting of approximately 50 transcription factors implicated in many biological function. It is an essential nuclear receptor controlling the expression of a large number of regulatory genes in lipid metabolisms, insulin sensitization, inflammation, and cell proliferation [48].

Similarly to other nuclear hormone receptors, PPARγ displays a central DNA-binding domain, a C-terminal ligand-binding domain, and two transcription-activation function motifs (AF-1 and AF-2) [49]. Binding of ligands to PPARγ leads to a conformational change in the receptor which allows recruitment of co-activator proteins to then induce transcriptional activation. The transcriptional activity of PPARγ is regulated by post-translational changes such as phosphorylation or ubiquitination. The activation requires heterodimerization within the nucleus with another nuclear receptor named retinoid X receptor α (RXRα), leading to bind a specific DNA sequence elements known as peroxisome proliferator elements (PPREs) [50]. PPARγ interferes with inflammatory pathways by interactions with transcription factors such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), signal transducer and activator of transcription (STAT), and nuclear factor-activated T cell (NFAT). For example, PPARγ is able to form a complex with the NF-κB subunit p65 at a nuclear level and this complex is exported from the nucleus leading to an altered expression of proinflammatory NF-κB-mediated gene expression. Inhibition of NF-κB in response to the activity of PPARγ ligands attenuates the expression of various cytokines in colonic epithelial cells such as IL-1β, COX-2, IL-6, IL-8, TNF-α, INF-γ, iNOS, and chemokines [51, 52]. Its expression has been initially investigated in adipose tissue where it plays a key role in adipocyte differentiation and insulin responses. More recently the colon has been found to highly express PPARγ in epithelial cells but also macrophages and lymphocytes [16, 52, 53]. Regulation of expression is incompletely understood; in vivo mRNA expression is negatively influenced by a long-term hypocaloric diet and fasting and positively by obesity and a rich in fatty acids diet. More recently a close link between intestinal microbial flora and PPARγ expression has been demonstrated. The stimulation of expression is probably multifactorial and involves the LPS recognition by the toll-like receptor (TLR), especially LPS of gram-negative bacteria and TLR4. Another alternative way of stimulation is the production through the bacteria of volatile fatty acid butyrate [15].

4. Experimental Model of Colitis

The initial evidence of the involvement of PPARγ in the regulation of intestinal inflammation derives from the observation of the use of PPARγ synthetic agonist thiazolidinedione (TZD) in mice dextran sodium sulfate- (DSS-) induced colitis. In the study by Su CG et al., both troglitazone and rosiglitazone dramatically reduced the colonic inflammation in mice and in addition significantly attenuated cytokine gene expression in colon cancer cell lines through NF-κB inhibition [21]. This first evidence was subsequently confirmed in another model of experimental colitis induced in mice by intrarectal administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) [51]. TZD given preventively significantly reduced mortality, severity of macroscopic and histological lesions, and markers of inflammation. So far several studies have reported similar prophylactic and therapeutic efficacy of PPARγ agonists in different animal models (mice, rats, and pigs) with different models of colitis induced by chemical compounds [22–34], ischaemia [35–38], bacteria [39], or genetically modified animals [43–47, 65, 66] (Table 1) [40–42]. Moreover a beneficial effect of PPARγ ligands has been demonstrated in colon carcinogenesis. Of interest, the use of probiotics (VSL#3), conjugated linoleic acid, n-3 polysaturated fatty acids, cannabidiol, punic acid, α-eleostearic acid, and a polyphenolic compound has prove beneficial effect on animal model of intestinal inflammation through the activation of PPARγ [67] (Table 1).

Taken together lessons from animal studies suggest that: (a) natural and synthetic PPARγ ligands are both effective in the treatment of acute and chronic animal models of inflammation; (b) the prophylactic effect is more pronounced than the therapeutic effect; (c) the therapeutic effect is apparently dependent by the abundance of PPARγ in the target tissue as demonstrated by the genetically modified animals. This information translated into clinical ground could suggest a major role of PPARγ agonists in maintenance rather than induction of remission in IBD patients. Moreover, with PPARγ being expressed not only in the epithelial cells but also in macrophages, T, and B cells, more investigations are needed to disclose which cell type expression of PPARγ is more crucial for the potential therapeutic effect.

5. Dietary Modulation of PPARγ

A large number of dietary nutrients are able to modulate PPARγ (see Table 2). Fatty acids and their metabolites can
Table 1: Anti-inflammatory properties of PPARγ agonists in experimental models.

| Model         | PPARγ modulator | Effect                          | Authors                                      |
|---------------|-----------------|---------------------------------|----------------------------------------------|
| Acute colitis | Troglitazone    | ↓ Colonic inflammation          | Su et al. 1999 [21]                          |
|               | Rosiglitazone   | ↓ Cytokine gene expression      |                                              |
|               | Pioglitazone    | Reduced inflammation More severe colitis Prevention colitis | Ramakers et al. 2007 [23] |
|               |                  | Prevention colitis              |                                              |
| DSS           | Rosiglitazone   | Reduced inflammation            | Saubermann et al. 2002 [22]                 |
|               | Pioglitazone    | Reduced inflammation            | Takagi et al. 2002 [24]                     |
|               |                  | Recovery from colitis           | Hontecillas et al. 2011 [25]                |
|               | PUFA            | Accelerated remission           |                                              |
|               | CLA             | Delayed onset of colitis        | Bassaganya-Riera 2006 [27]                  |
|               | CLA + VSL#3     | Improvement of colitis          | Bassaganya-Riera et al. 2012 [28]          |
|               | α-Eleostearic acid| Improvement of colitis         | Lewis et al. 2011 [29]                      |
| TNBS          | Troglitazone    | Reduced inflammation            | Desreumaux et al. 2001 [30]                |
|               | Rosiglitazone   | Reduced inflammation            |                                              |
|               | Pioglitazone    | Reduced inflammation            | Sánchez-Hidalgo et al. 2007 [31]           |
|               | FMOC-L-leu      | Reduced inflammation            | Rocchi et al. 2001 [32]                    |
|               | 5-ASA           | Reduced inflammation            | Rousseaux et al. 2005 [33]                 |
| 5-ASA in PPARγ+/− |            | No efficacy of 5-ASA           |                                              |
| Acetic acid   | THSG            | Attenuated colon lesions        | Zeng et al. 2011 [34]                       |
| ischaemia     | Rosiglitazone   | Protection                      | Nakajima et al. 2001 [35]                  |
|               | 15-d-PGJ2       | Reduced injury                  | Cuzzocrea et al. 2003 [36]                 |
|               | NS-398          | Protection                      | Sato et al. 2005 [37]                      |
|               | Glutamine       | Protection                      | Sato et al. 2006 [38]                      |
| Bacterial     | CLA             | Attenuated inflammation         | Hontecillas et al. 2002 [39]               |
| Chronic colitis| DSS             | Triglitazone                    | Tanaka et al. 2001 [40]                    |
|               | TNBS            | Rosiglitazone                   | Sánchez-Hidalgo et al. 2005 [41]           |
|               | CD4-CD45RBhi    | CLA                             | Bassaganya-Riera et al. 2004 [42]          |
|               | IL-10 KO        | Rosiglitazone Slow onset colitis | Lytle et al. 2005 [43]                     |
|               | SAMP1/Yirfca    | Rosiglitazone Decreased severity | Sugawara et al. 2005 [44]                  |
| Genetic models | Ischaemia       | More severe damage              | Desreumaux et al. 2001 [30]                |
|               | PPARγ +/-       |                                 | Nakajima et al. 2011 [35]                  |
|               | DSS + PUA       | Loss protective effect PUA      | Hontecillas et al. 2011 [25]               |
|               | AdPPARγ         |                                 | Katayama et al. 2003 [39]                  |
|               | SAMP1/yirfca    |                                 | Sugawara et al. 2005 [44]                  |
|               | PPARγCre+       |                                 | Bassaganya-Riera et al. 2004 [42]          |
|               | PPARγΔMϕ       | DSS Increased susceptibility    | Shah et al. 2007 [45]                      |
|               | PPARγfifi       | DSS Accelerated colitis         | Guri et al. 2010 [46]                      |
|               |                 |                                 | Mohapatra et al. 2010 [47]                 |

5-ASA: 5-aminosalicylic acid; 15dPGJ2: 15-deoxy-A12,14-prostaglandin J2; CLA: conjugated linoleic acid; PUFA: n-3 polyunsaturated fatty acids; DSS: dextran sodium sulphate; FMOC-L-leu: fluorenylmethoxy carbonyl-L-leucine; IL-10 KO: interleukin 10 knockout mice; PPARγCre: PPARγ conditional knockout mice; TNBS: 2,4,6-trinitrobenzene sulfonic acid; PUA: punicic acid; THSG: 2,3,5,4′-tetrahydroxystilbene-2-O-beta-D-glucoside.
The majority of patients with UC for the induction of remis-
treatment of IBD, although the mechanism underlying its
5-ASA is one of the oldest anti-inflammatory agents used for
6. PP AR

shown activation property on PPAR γ acid (CLA), nitrolinoleic acid, and gamma linoleic acid have
in human diet and several derivatives like conjugated linoleic
γ by a PPAR γ acid-derived metabolite known to be a strong PPAR
γ [56–58]. Also ginsenosides, compounds derived by ginseng, may have opposite e
γ [59, 60]. Finally, other inducers are flavonoids,

Since in animal models treatment with PPARγ ligands has been demonstrated to attenuate inflammatory cytokines production such as IL-1β and TNF-α, it has been hypothe-
sized the use of PPARγ ligands, like thiazolidinedione (TZD), in the therapy of UC [15]. One potential candidate is rosigli-
tazone, an antidiabetic drug. A first open-label pilot study
in patients with mild to moderate UC refractory to 5-ASA
has evaluated the efficacy of the PPARγ ligand rosiglitazone
(4 mg orally twice daily) (Table 3). These patients were
refractory to conventional treatment, including corticos-
steroids and immune modulators. After 12 weeks of treat-
ment, a striking reduction in disease activity index score was
reported, with clinical and endoscopic remission in 27% and
20% of patients, respectively [68]. Liang and Quayang
performed a clinical trial in China in 42 patients with mild to
moderate UC [69]. Patients were allocated alternatively to the
administration of rosiglitazone 4 mg/day plus 5-ASA 2 gr or sul-
fasalazine 3 gr, while the control group received 5-ASA or sul-
fasalazine alone for 4 weeks. The remission rate was greater
in the rosiglitazone group (71.4% versus 57.1%), with a
significant improvement of the histologic score (P < 0.05).
Moreover in the treatment group the PPARγ expression was
increased compared to baseline [69].

6. PPARγ and Therapy of Ulcerative Colitis

5-ASA is one of the oldest anti-inflammatory agents used for
treatment of IBD, although the mechanism underlying its
effects is still unknown. It is the mainstay of therapy for
the majority of patients with UC for the induction of remis-
sion, maintenance, and possibly chemoprevention of col-
rectal cancer [73]. Recently, functional, biological, pharma-
cological, and chemical evidence has shown that aminosal-
icylates are a new functional synthetic ligand for PPARγ in
colonic epithelial cells [33]. PPARγ is indeed the key receptor
mediating the 5-ASA activity, by trans-repressing several key
target genes such as nuclear factor κB, signal transducers, and
activators of transcription.

Table 2: Nutrients with demonstrated anti-inflammatory effects mediated through PPARγ.

| Nutrient              | Dietary source               | Models                          | Authors                        |
|-----------------------|------------------------------|---------------------------------|--------------------------------|
| α-linoleic acid       | Green vegetables, flax       | Intestinal epithelial cells     | Marion-Letellier 2008 [54]    |
| Docosahexaenoic acid  | Fish                         | Intestinal epithelial cells     | Marion-Letellier 2008 [54]    |
| Eicosapentaenoic acid | Beef, bovine milk            | Intestinal epithelial cells     | Alred et al. 2008 [55]         |
| Conjugated linoleic acid | Beef, bovine milk           | Intestinal epithelial cells DSS colitis | Sato et al. 2006 [38] |
| Glutamine             | Beef, chicken, fish          | Ischaemia reperfusion           | Salh et al. 2003, Deguchi et al. 2007 [56] [57] |
| Curcumin              | Tumeric powder               | TNBS colitis                    | Kim et al. 2004 [58]           |
| Capsaicin             | Cayenne pepper               | Intestinal epithelial cells     | Han et al. 2006, Hwang et al. 2007 [59] [60] |
| Ginsenosides          | Ginseng                      | Adypocites                      | Schub et al. 2007 [62]         |
| Resveratrol           | Grapes, wine, peanuts        | Intestinal epithelial cells     | Morikawa et al. 2007 [61]      |
| Butyrate              | Unabsorbed carbohydrate      | Intestinal epithelial cells     | Sato et al. 2006 [38]          |
| Vitamin E             | Nuts, seeds, oils            | Colon cancer cell lines         | Campbell et al. 2003 [63]      |
| Selenium              | Plant foods                  | Macrophages                     | Yunta et al. 2007 [64]         |

Table 3: Efficacy of rosiglitazone therapy in ulcerative colitis (*P values < 0.05).

| Authors               | N pts | Study design | Treatment | Response | % Efficacy Remission | % Efficacy Mucosal healing |
|-----------------------|-------|--------------|-----------|----------|----------------------|---------------------------|
| Lewis et al. 2001 [68] | 15    | Open 12 weeks | 4 mg tid  | —        | 27                   | 20                        |
| Liang and Quayang 2006 [69] | 42    | Random versus 5-ASA | 4 mg | —        | 71 versus 57*         | —                        |
| Lewis et al. 2008 [70]  | 105   | 12 wks versus Plac  | 4 mg tid  | 44 versus 23* | 17 versus 2*          | 8 versus 2                |
| Pederson and Bryanskov 2010 [71] | 14    | Open versus 5-ASA | 4 mg versus 1 enema | 5-ASA | 5-ASA | — |
Recently, a randomized multicenter double-blind, placebo-controlled trial has been published by using rosiglitazone 4 mg orally twice daily versus placebo for 12 weeks in 105 patients with mild to moderate ulcerative colitis [70]. Disease activity was measured by Mayo score with a primary endpoint of a clinical response (≥2 points reduction) at week 12, while clinical remission, endoscopic remission, and quality of life changes were considered secondary outcomes. After 12 weeks of therapy, 23 patients (44%) treated with rosiglitazone and 12 patients (23%) treated with placebo achieved clinical response ($P = 0.04$). Remission was achieved in 9 patients (17%) treated with rosiglitazone and 1 patient (2%) of the placebo arm ($P = 0.01$). However, endoscopic remission was uncommon in either arms (8% versus 2%; $P = 0.34$). Clinical improvement was clearly evident already at 4 week ($P = 0.049$), while quality of life was significantly improved at week 8 ($P = 0.01$), but not at week 4 and 12. The safety profile was remarkably safe, with adverse events occurring at similar rates in both groups; in particular edema and weight gain, as expected, were more common in the rosiglitazone group. Of interest, no cases of symptomatic hypoglycemia were reported.

Pederson and Brynskov reported the use of rosiglitazone enema compared to mesalazine in fourteen patients with distal UC [71]. Rosiglitazone had a similar effect compared to mesalazine enema, with a significant reduction of Mayo score ($P < 0.01$). In addition rosiglitazone restored the PPARγ activity in the inflamed area which was fourfold reduced before treatment compared with noninflamed areas and controls.

Although substantial research has focused on potential anti-inflammatory effects of TZD PPARγ ligands, their mechanism of action, particularly in the colon, is not well defined. The 5-ASA compounds largely used in UC are able to bind to PPARγ [33]. In the study of Lewis et al. [70] the majority of patients were on concomitant therapy with 5-ASA. Since rosiglitazone has a higher affinity to PPARγ compared to 5-ASA, one possible explanation of the efficacy is a more powerful stimulation and anti-inflammatory property of PPARγ. Alternatively, the effect could be mediated at the mucosal level, where the PPARγ is largely expressed [74]. Of note, large clinical trials with rosiglitazone in the treatment of psoriasis, another inflammatory disease, did not demonstrate efficacy, thus suggesting a “topical” and not a systemic effect in patients with UC [75].

Being also involved in cell proliferation, apoptosis, and modulation of cytokine production with antitumorigenic effect, PPARγ is also extremely important for the basis of chemoprevention strategies against colorectal cancer. For these reasons, there is an active ongoing research to disclose and investigate safer PPARγ agonists, with topical effect and direct targeting of the colon, possibly void of metabolic and systemic effect.

7. PPARγ and Therapy of Crohn’s Disease

Recent data have suggested that the role of PPARγ in IBD physiopathology is not limited to UC but might involve also CD. Based on SAMP1/YitFc animal example, developing a spontaneous ileitis due to a defect of expression of PPARγ in ileal crypts, the polymorphisms of PPARγ has been tested in CD. Sugawara et al. [44] demonstrated that two intronic SNPs exhibited a significant lower frequency in CD compared to controls. However, these findings have not been independently replicated yet. Moreover, no data are available by using PPARγ ligands in medical therapy of CD, in which 5-ASA compounds are generally believed to be of little or no efficacy [73].

8. Conclusion and Take-Home Messages

PPARγ receptors are widely and highly expressed in the colon, being a key regulator factor of bacteria-induced mucosal inflammation. Moreover, they are directly involved in the mechanism of action of mesalazine, which is largely used and effective in UC. In addition, they are involved in the process of tumor suppression, especially in the colon. Therefore, beside the potential interest in the IBD physiopathology and genetic predisposition which is still under evaluation, it is highly expected that new molecules specifically targeting the intestinal receptors and void of action in the adipose tissue and insulin action could be developed and tested. Several tens of compounds have been already synthetized, some with 30–50-fold higher affinity against PPARγ and potentially higher efficacy than 5-ASA. These compounds are not that far from clinical application with potential implication in controlling the inflammation, better handling of host-bacterial interactions, and possible chemoprevention. In addition, a better understanding of the role of microbiota on PPARγ receptors should be elucidated, since some commensal bacterial or natural ligands of foods may directly activate and increase the expression of PPARγ, thus determining a “biologic” anti-inflammatory action.

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