



Peroxisome proliferator-activated receptors in inflammatory bowel disease: linking immunometabolism, lipid signaling, and therapeutic potential

Kiandokht Bashiri^{1,2}, Mark C. Mattar¹, Alireza Meighani¹, Andrew L. Mason²

¹Department of Gastroenterology, MedStar Georgetown University Hospital, Washington, DC, USA; ²Department of Medicine, Center of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta, Edmonton, AB, Canada

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis, is a chronic condition marked by immune dysregulation, genetic predisposition, and metabolic disturbances. Emerging evidence highlights the role of lipid metabolism and peroxisome proliferator-activated receptor (PPAR) signaling in modulating immune responses in IBD. PPAR- γ and PPAR- α regulate macrophage polarization, T-cell differentiation, and epithelial barrier integrity, influencing disease severity and progression. Alterations in PPAR activity contribute to metabolic stress and inflammation, linking IBD pathophysiology to immunometabolism. Studies suggest that targeting PPARs may mitigate inflammation through modulation of cytokine production, immune cell function, and gut microbiota interactions. In this review, we focus specifically on CD and explore how PPAR signaling intersects with mesenteric adipose tissue dysfunction and microbial dysbiosis, 2 hallmark features of CD. PPAR agonists, already used in metabolic-inflammatory diseases such as metabolic-associated liver disease, have demonstrated anti-inflammatory effects in experimental colitis models. Translating these findings into clinical applications could offer novel treatment strategies for CD. Future research should focus on clinical trials, genetic studies, and microbiota-targeted approaches to elucidate PPAR-driven mechanisms in CD pathogenesis. Understanding the interplay between PPARs, lipid metabolism, and immune responses may lead to innovative therapeutic strategies, improving disease management and patient outcomes. (Intest Res 2026;24:11-26)

Key Words: Crohn disease; Peroxisome proliferator-activated receptors; Immunometabolic phenomena; Lipid metabolism; Inflammation

INTRODUCTION

Inflammatory bowel disease (IBD), manifests as chronic inflammation across various sections of the gastrointestinal tract. Disease activity is influenced by multiple factors, including genetic predisposition, environmental triggers, alterations in gut microbiota, and immune dysregulation.¹ Recent insights into immunometabolism have revealed that metabolic processes

within immune cells play a critical role in disease pathogenesis, linking metabolic dysregulation to immune responses in chronic inflammation.² Dysregulation in lipid metabolism, mediated by pathways such as peroxisome proliferator-activated receptor (PPAR) signaling, plays a critical role in immune cell function and inflammatory responses in IBD and other metabolic-inflammatory conditions. Lipid metabolism influences key processes such as macrophage polarization, T-cell differentiation, and epithelial barrier integrity, which are central to Crohn's disease (CD) pathophysiology.³ For example, in metabolic-associated liver disease, dysregulated lipid metabolism contributes to inflammation and immune dysregulation

Received May 29, 2025. Revised June 30, 2025. Accepted July 7, 2025.

Correspondence to Kiandokht Bashiri, Department of Gastroenterology, MedStar Georgetown University Hospital, 3800 Reservoir Rd NW, Washington, DC 20007, USA. E-mail: kiandokh@ualberta.ca

Table 1. Key Features of PPAR α , PPAR β/δ , and PPAR γ ⁵⁻¹⁰

Feature	PPAR α	PPAR β/δ	PPAR γ
Tissue expression	Liver, heart, muscle, intestine	Ubiquitous (muscle, gut, adipose)	Adipose tissue, colon, immune cells
Endogenous ligands	Fatty acids, eicosanoids	Unsaturated fatty acids, 15-HETE	15d-PGJ2, oxidized lipids
Synthetic ligands	Fibrates (e.g., fenofibrate)	Seladelpar, GW501516 (research use)	TZDs (e.g., rosiglitazone, pioglitazone)
Main functions	Fatty acid oxidation, lipid catabolism	Energy expenditure, lipid metabolism	Adipogenesis, insulin sensitization
Immune role	Anti-inflammatory, promotes M2 macrophages	Suppresses M1, supports immune balance	Strongly anti-inflammatory, M2 polarization
Associated diseases	Dyslipidemia, NAFLD, atherosclerosis	Metabolic syndrome, NAFLD	T2D, obesity, IBD, NASH

PPAR, peroxisome proliferator-activated receptor; 15-HETE, 15-hydroxyeicosatetraenoic acid; 15d-PGJ2, 15-deoxy-delta-12,14-prostaglandin J2; TZD, thiazolidinedione; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes; IBD, inflammatory bowel disease; NASH, nonalcoholic steatohepatitis.

through ectopic fat deposition, lipotoxicity, and the accumulation of toxic lipid species like ceramides and diacylglycerols.⁴

PPARs, a family of nuclear receptor transcription factors, regulate lipid metabolism, energy homeostasis, and immune responses. PPARs exist in 3 isoforms: PPAR α , PPAR β/δ , and PPAR γ , each encoded by distinct genes and exhibiting tissue-specific expression (Table 1).⁵⁻¹⁰ PPARs function by forming heterodimers with the retinoid X receptor and binding to PPAR response elements in the promoter regions of target genes. Upon ligand binding, PPARs recruit co-activators or co-repressors to regulate gene transcription. In immune cells, PPAR activation can suppress pro-inflammatory pathways such as nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1) while promoting lipid-catabolic and oxidative metabolic programs.¹¹ Given these functions, PPARs serve as molecular bridges between metabolic cues (like fatty acids or eicosanoid ligands) and immune cell behavior.^{7,8,11-14} In this review, we examine the role of PPAR signaling in the pathogenesis and regulation of IBD, with a particular focus on CD. We explore how PPAR isoforms—especially PPAR γ —modulate immune cell phenotypes, maintain epithelial barrier integrity, and influence the inflammatory environment within the gut.

IMMUNOMETABOLIC DYSREGULATION IN CD

CD is fundamentally an immune-mediated disorder, but its pathogenesis cannot be fully explained without considering metabolic context. Immunometabolism refers to how cellular metabolism governs immune cell function and fate. In CD lesions, immune cells exist in a nutrient- and oxygen-deprived milieu, forcing metabolic adaptations that can intensify inflammation. For example, classically activated M1 macrophages

(abundant in active CD) rely on aerobic glycolysis and broken tricarboxylic acid cycle activity to sustain rapid cytokine production, whereas anti-inflammatory M2 macrophages use oxidative metabolism and fatty-acid β -oxidation.¹¹ In CD, the persistent presence of microbial antigens and cytokines (e.g., interferon γ [IFN- γ], tumor necrosis factor α [TNF- α]) drives macrophages toward the pro-inflammatory M1 state, accompanied by metabolic reprogramming that favors glycolytic energy production and lipid droplet accumulation. Similarly, effector T cells in the inflamed gut favor glycolysis, while regulatory T cells and memory T cells depend more on lipid oxidation and mitochondrial respiration. These metabolic programs are tightly linked to the cells' inflammatory outputs—an emerging paradigm is that tweaking cellular metabolism can modulate immune responses in IBD.

The intestinal microenvironment in CD further reflects this immunometabolic imbalance. Mucosal tissues from CD patients often show an altered lipid profile and energy metabolism signature. Mesenteric adipose tissue hypertrophies into “creeping fat” around areas of transmural inflammation, indicating a redistribution of lipid storage and metabolism to the intestinal vicinity. This creeping fat is not inert; it secretes adipokines like leptin and adiponectin, and pro-inflammatory mediators, which can influence immune cell polarization and fibrosis in the gut. Notably, creeping fat adipocytes exhibit changes in their metabolic gene expression. Single-cell transcriptomic studies have identified a subpopulation of stromal cells within creeping fat that highly expresses lipoprotein lipase and shows elevated transcriptional activity of PPAR γ and related lipid metabolic pathways.^{15,16} This suggests that PPAR γ -driven lipid metabolism in creeping fat may be a response to—or contributor to—intestinal inflammation, potentially by supplying energy-rich lipids or antimicrobial molecules to the in-

flamed gut wall (e.g., through upregulation of lipid-handling and antibacterial genes). Thus, metabolic reprogramming is intertwined with immune regulation in CD at both the cellular and tissue level.

PPARs are central to immunometabolic regulation, making them well-positioned to influence CD processes. As lipid sensors, PPARs respond to fatty acids, eicosanoids, and other metabolites that accumulate in inflamed or hypoxic tissues. Activation of PPAR α or PPAR γ can recalibrate the metabolism of macrophages and T cells: for instance, PPAR activation promotes β -oxidation of fatty acids and dampens glycolytic flux, which can push macrophages toward a more restorative M2 phenotype and encourage T cells towards regulatory or less inflammatory states.¹⁷ In parallel, PPAR signaling directly suppresses pro-inflammatory gene transcription (via transrepression of NF- κ B, AP-1, and other pathways) and induces genes involved in cellular stress defense (such as antioxidant enzymes and anti-apoptotic factors). These effects exemplify how manipulating metabolism can have downstream immune consequences. Indeed, loss-of-function models have shown that without PPARs enforcing metabolic checks, inflammation is amplified: mice lacking PPAR α develop a heightened Th1/Th17 response to commensal microbiota and suffer more severe colitis.^{18,19}

Moreover, immunometabolic perturbations in CD extend to the epithelial barrier, where energy metabolism influences barrier integrity and mucus production. Butyrate—a short-chain fatty acid (SCFA) produced by gut microbiota—is a prime example of an immunometabolic mediator: it serves as the primary fuel for colonic epithelial cells and also exerts anti-inflammatory effects. Butyrate has been shown to enhance intestinal barrier function by acting on epithelial cell metabolism and by activating PPAR γ . In colonic epithelial models, butyrate upregulates PPAR γ and stimulates PPAR-responsive genes, thereby tightening junctional complexes and reducing permeability. In active CD, where butyrate-producing microbes are often depleted, reduced PPAR γ activity in epithelial cells may contribute to barrier defects and increased translocation of luminal antigens.²⁰ This example illustrates how microbial metabolites, PPAR signaling, and immune activation form a triad critical to gut homeostasis. In summary, CD can be viewed as a state of pathologic immunometabolism, and PPARs represent nodal points in the network of metabolic and inflammatory pathways. We next examine each PPAR isoform's specific roles in the context of CD.

PPAR γ : MODULATING INFLAMMATION, BARRIER FUNCTION, AND FIBROSIS

PPAR γ is the most extensively studied PPAR isoform in IBD and is highly expressed in colonic epithelial cells, adipocytes, and immune cells of the gut mucosa.²¹ It functions as a master regulator of adipogenesis and has potent anti-inflammatory properties in immune cells. PPAR γ 's role in CD is multifaceted, affecting immune cell polarization, cytokine responses, intestinal barrier maintenance, and fibrotic remodeling.

1. Regulation of Mucosal Immunity

PPAR γ serves as an important brake on inflammatory myeloid cells. In macrophages, ligand-activated PPAR γ transrepresses inflammatory gene expression—it can interfere with NF- κ B and signal transducer and activator of transcription 1 (STAT1) signaling and promote an alternative activation state (M2) characterized by secretion of interleukin (IL)-10 and transforming growth factor β (TGF- β) rather than TNF- α and IL-12.^{22,23} *In vivo* evidence comes from murine IBD models: mice engineered to lack PPAR γ in myeloid cells develop markedly exacerbated colitis with high levels of IFN- γ , enhanced expression of Toll-like receptor (TLR) co-stimulatory molecules, and an accumulation of inflammatory Ly6Chi monocytes.^{24,25} Similarly, T cell-specific PPAR γ knockout leads to accelerated colitis, with increased Th1/Th17 cytokines (IL-6, IL-1 β) and loss of regulatory T cells.^{26,27} These findings demonstrate that PPAR γ in both innate and adaptive immune compartments restrains pathogenic inflammation in the gut. Mechanistically, PPAR γ activation in T cells has been linked to suppression of SOCS3 and NF- κ B-dependent apoptotic pathways, as well as preservation of FoxP3+ regulatory T cells.^{11,26} Thus, PPAR γ acts as an immunoregulatory factor, helping to maintain tolerance to commensals and preventing overactive immune responses in the intestine.

2. Maintenance of Epithelial Integrity

PPAR γ is expressed by intestinal epithelial cells (especially in the colon), where it contributes to barrier function and anti-inflammatory signaling. PPAR γ activation promotes differentiation of goblet cells and enhances the expression of tight junction proteins, partly via upregulating genes that support mucosal repair and by transcriptional suppression of inflammatory cascades within epithelial cells. In mice with epithelial-specific PPAR γ deletion, the colonic epithelium is more susceptible to injury: experimental colitis causes more severe

erosions and ulceration in these mice, accompanied by greater leukocyte infiltration.²⁸ Interestingly, the impact of epithelial PPAR γ loss on clinical colitis indices was strain-dependent in studies (significant in C57BL/6 background), but in all cases there was evidence that epithelial PPAR γ helps limit inflammatory damage.^{28,29} One way PPAR γ might protect the epithelium is through influencing immune-epithelial cross-talk—for example, PPAR γ in epithelial cells can affect the cytokine milieu (such as IL-10 levels in local lymph nodes) that in turn shapes T cell responses. In summary, PPAR γ helps maintain the integrity of the gut lining, making it harder for bacteria and antigens to provoke inflammation.

3. Anti-Fibrotic Effects

CD often leads to transmural fibrosis and stricture formation due to chronic wound-healing responses. PPAR γ has emerged as a negative regulator of fibrogenesis in the gut. This stems from PPAR γ 's ability to antagonize TGF- β /Smad signaling, the central pathway driving collagen deposition and myofibroblast activation. Indeed, PPAR γ agonists inhibit the differentiation of intestinal fibroblasts into collagen-secreting myofibroblasts *in vitro*.^{22,30,31} In other organs, PPAR γ ligands have been shown to upregulate anti-fibrotic genes (e.g., matrix metalloproteinases) and downregulate collagen I, and similar mechanisms likely apply in intestinal fibrosis.³² In a murine model of chronic TNF-driven ileitis, PPAR γ activation was found to reduce fibrotic stricture severity by suppressing profibrotic gene expression (such as α -smooth muscle actin and collagen).^{33,34} Clinically, while anti-fibrotic therapy in CD remains an unmet need, these insights position PPAR γ as a promising target for preventing or treating strictures. It is notable that standard IBD drugs 5-aminosalicylic acid (5-ASA) compounds activate PPAR γ —this is thought to contribute to their anti-inflammatory effect, though 5-ASA alone does not reverse established fibrosis.^{35,36} A specially designed 5-ASA derivative (GED-0507, a partial PPAR γ agonist) showed anti-fibrotic potential in pre-clinical studies, but a clinical trial in CD strictures was halted due to recruitment issues.^{11,33}

4. Evidence in IBD Patients

Translational studies provide hints that PPAR γ activity is perturbed in IBD. In ulcerative colitis (UC), PPAR γ expression is markedly diminished in inflamed colonic mucosa—one landmark study showed PPAR γ mRNA and protein levels in UC patient biopsies were drastically lower than in healthy controls (and even lower than in CD biopsies).^{5,37} This finding aligns

with clinical observations that PPAR γ agonists (like rosiglitazone) have moderate efficacy in UC. In CD, the reduction of PPAR γ appears more nuanced. Several studies have reported that colonic PPAR γ mRNA is significantly downregulated in both active CD and UC.^{38–40} Another cohort study found that PPAR γ levels in non-inflamed areas of CD patients were relatively preserved, and that PPAR γ expression did not correlate with CD severity or location, in contrast to UC where it tracked disease activity.³⁹ These data suggest that while PPAR γ is involved in CD pathogenesis, its impairment is less uniform than in UC. Genetic studies echo this pattern: the common functional variant PPAR γ Pro12Ala (rs1801282), which reduces PPAR γ activity, is linked with susceptibility to UC but less associated to CD.^{41,42} The lack of a strong genetic association in CD implies that PPAR γ dysfunction in CD is likely context-driven (e.g., due to inflammation or microbial products) rather than primary.¹¹ Importantly, even if not a primary risk gene, PPAR γ remains a critical node that can be therapeutically leveraged to modulate downstream inflammation.

5. Summary

In summary, PPAR γ in the gut orchestrates a wide array of protective functions: it tempers innate and adaptive immune activation, bolsters the epithelial barrier, and counteracts fibrosis. Insufficient PPAR γ activity—whether through genetic predisposition, inhibitory post-translational modifications, or overwhelming inflammatory signals—can remove these brakes, exacerbating the chronic inflammation of CD. The therapeutic implications of this are discussed later; notably, PPAR γ agonists are being explored as a means to reinforce these endogenous anti-inflammatory pathways in IBD.

PPAR α : INTEGRATING LIPID METABOLISM WITH MUCOSAL IMMUNITY

PPAR α is classically known for its role in hepatic lipid oxidation and fasting metabolism, but it is also expressed in the gastrointestinal tract and immune cells where it has significant immunomodulatory effects. In the small intestine, PPAR α is present at high levels in the duodenum/jejunum and in various hematopoietic cells including monocytes, macrophages, and dendritic cells.⁴³ PPAR α activation drives transcription of genes for fatty acid β -oxidation (e.g., acyl-CoA oxidase, CPT1) and simultaneously exerts anti-inflammatory actions.⁴⁴ In CD, where an imbalance of pro- and anti-inflammatory lipid mediators is evident, PPAR α plays a pivotal regulatory role.

1. Host Defense and Tolerance to Microbiota

Elegant studies have shown that PPAR α is indispensable for maintaining immune homeostasis in the gut in the face of the microbiota. PPAR α -knockout mice exhibit an exaggerated inflammatory reaction to commensal bacteria, resulting in spontaneous or more severe induced colitis.⁴⁵⁻⁴⁷ This dysregulated response is partly due to PPAR α 's role in constraining Th1/Th17 polarization—PPAR α -/- mice have an expansion of Th1 and Th17 cells in the colon, along with higher levels of pro-inflammatory cytokines, which can be ameliorated by antibiotic depletion of the microbiota. One critical cytokine influenced by PPAR α is IL-22, produced by innate lymphoid cells (ILC3) and Th22 cells. IL-22 is essential for epithelial barrier integrity and antimicrobial peptide production. In PPAR α deficiency, IL-22 levels are reduced, compromising epithelial defense.¹⁷ Thus, PPAR α helps calibrate the mucosal immune system's interaction with gut bacteria—it promotes tolerance and balanced immune responses, preventing the overactivation that characterizes IBD.

2. Inflammatory Pathway Modulation

At the molecular level, PPAR α activation directly antagonizes key inflammatory signaling pathways. PPAR α can physically interact with transcription factors like NF- κ B p65 and AP-1 (c-Jun), acting as a transcriptional sink that blunts their ability to induce pro-inflammatory genes.^{48,49} For instance, PPAR α agonists suppress IL-6 and TNF- α production in activated monocytes and adipocytes by these transrepression mechanisms.⁵⁰ PPAR α also facilitates the catabolism of inflammatory lipid mediators.⁶ In PPAR α -null mice, this catabolic pathway is absent and LTB4-driven neutrophilic inflammation is unchecked—indeed, PPAR α -/- mice cannot efficiently resolve inflammation mediated by LTB4 and related mediators.⁵¹ Furthermore, PPAR α suppresses Th1 differentiation by downregulating T-bet (the master transcription factor for Th1) via inhibition of p38 mitogen-activated protein kinase (MAPK) phosphorylation.⁵² Through such mechanisms, PPAR α activation broadly attenuates both innate and adaptive inflammatory circuits that are active in CD.

3. Effects on Epithelial Cells and Barrier

While PPAR α is less abundant in colonic epithelial cells than PPAR γ , it is present in small intestinal epithelium and may contribute to barrier function indirectly. PPAR α activation in macrophages and ILC3 leads to higher IL-22, which, as noted, strengthens the epithelial layer by inducing antimicrobial pep-

tides and mucins.⁵³ Additionally, some metabolites that activate PPAR α have been shown to improve epithelial integrity. Palmitoylethanolamide (PEA), a naturally occurring fatty acid ethanolamide and PPAR α agonist, is elevated in inflamed intestinal tissues, perhaps as an endogenous protective response.⁵⁴ Supplementation with PEA in mice reduced experimental colitis severity and improved gut permeability.⁵⁵ Notably, PEA's anti-inflammatory benefit was lost if PPAR α was pharmacologically or genetically blocked, confirming that PPAR α mediates a significant part of PEA's effect.^{56,57}

4. CD and PPAR α in Humans

Similar to PPAR γ , PPAR α -related pathways are perturbed in IBD patients. Integrative-omics analyses have identified that genes under PPAR α regulation are downregulated in IBD mucosa compared to healthy mucosa.³ This likely reflects the inflammatory milieu down-modulating metabolic genes. Clinically, indirect evidence points to PPAR α 's importance: for example, therapy with statins (HMG-CoA reductase inhibitors that also upregulate PPAR α expression in liver and macrophages) has been associated with reduced risk of developing CD in epidemiological studies.^{52,58} Moreover, in patients with established IBD, those on statins have shown decreased progression to surgery, hinting at a beneficial modulation of disease course.⁵⁹ While confounding factors exist, these observations align with the idea that PPAR α activation exerts anti-inflammatory and possibly anti-fibrotic effects in CD.

5. Preclinical Therapeutic Studies

PPAR α agonists (fibrate drugs) have been tested in animal IBD models with promising, though sometimes conflicting, results. In IL-10 knockout mice (a spontaneous colitis model marked by Th1/Th17 excess), the PPAR α agonist fenofibrate significantly reduced colonic inflammation, lowering IFN- γ and IL-17 levels and ameliorating histopathology.⁶⁰ This suggests activating PPAR α can rein in pathogenic T cell responses. Conversely, a study in acute dextran sulfate sodium (DSS) colitis reported that fenofibrate worsened inflammation and epithelial injury via PPAR α -dependent changes in lipid metabolism (e.g., altered ceramide/sphingolipid levels leading to epithelial cell necrosis).⁶¹ The discrepancy likely owes to differences between chronic versus acute models and highlights that PPAR α 's effects might vary with context (timing, cellular target, and presence of certain lipids). Nonetheless, the overall evidence supports an anti-inflammatory role for PPAR α , and interest has translated to clinical trials: fibrates are currently

being repurposed in early-phase trials for UC (as adjunct therapy), and similar approaches may extend to CD if safety and efficacy signals are positive.⁶² Importantly, DSS results are a proxy for IBD but not specific to CD pathology. Further studies using CD models demonstrating transmural inflammation (e.g., IL-10^{-/-}, SAMP1/YitFc, TNF^{ΔARE} mice) are warranted to confirm potential translation of PPAR-based interventions to CD.

6. Summary

In conclusion, PPAR α serves as an important immunometabolic checkpoint in the gut. It connects the sensing of nutritional and microbial-derived lipids to appropriate immune responses—promoting lipid catabolism and dampening excessive inflammation. In CD, enhancing PPAR α activity represents a logical strategy to restore metabolic-immune balance, by clearing pro-inflammatory lipid mediators, bolstering epithelial defenses, and limiting pathogenic T cell responses. Any future therapy targeting PPAR α will need to carefully navigate its complex biology (to avoid unwanted metabolic side effects), but the potential to “reset” mucosal immunity via metabolic modulation is a compelling avenue in IBD research.

PPAR β/δ : EMERGING INSIGHTS INTO INTESTINAL HOMEOSTASIS

PPAR β/δ , also referred to as PPAR δ , remains the least explored of the PPAR isoforms in the context of CD, yet emerging research highlights its significant influence on intestinal homeostasis and potential relevance to CD pathology. PPAR δ is expressed broadly, including in colonic epithelial cells, immune cells, and even Paneth cells of the small intestine.⁴⁵ It is a potent regulator of processes like fatty acid metabolism and cellular differentiation. While much attention has focused on its roles in metabolic disorders and cancer, its contributions to gut physiology are now coming into focus. Below, we explore PPAR δ 's multifaceted roles in intestinal immunity, epithelial function, and T cell metabolism, alongside considerations for its therapeutic potential in CD.

1. Macrophage Polarization

PPAR δ plays a nuanced role in regulating macrophage behavior, distinct from the predominantly anti-inflammatory effects of PPAR α and PPAR γ . Its impact on macrophage polarization depends on the cellular context and ligand activation. When activated by agonists, PPAR δ can suppress pro-inflammatory

cytokine release by disrupting its interaction with the transcriptional repressor B-cell lymphoma 6 (BCL-6). In its unliganded state, PPAR δ associates with BCL-6 to inhibit anti-inflammatory gene expression, but ligand binding releases this suppression, allowing PPAR δ to curb inflammatory pathways.⁶³ Additionally, CD137 signaling also induces M2 polarization through the STAT6/PPAR δ pathway.⁶⁴

2. Paneth Cell Function and Microbiota Composition

One of the most intriguing roles of PPAR δ is in Paneth cells, the specialized epithelial cells at the base of small intestinal crypts that secrete defensins and shape the microbiome. CD (particularly ileal CD) is associated with Paneth cell dysfunction and reduced antimicrobial peptide secretion, leading to dysbiosis. One study showed that PPAR δ is a key regulator of Paneth cell differentiation via interactions with the Hedgehog signaling pathway.⁶⁵ Mice lacking PPAR δ had significantly fewer Paneth cells and diminished expression of defensins. Consequently, these PPAR δ -deficient mice harbored an altered gut microbiota.^{65,66} Given that ileal CD is characterized by defective Paneth cells and an expansion of adherent invasive bacteria, PPAR δ loss could be a contributing factor to this phenotype. Conversely, ensuring adequate PPAR δ activity might preserve Paneth cell numbers and their microbial control function, thereby preventing dysbiotic triggers of inflammation.

3. Metabolic Reprogramming of T Cells

PPAR δ has been implicated in the metabolism of T lymphocytes as well. Memory CD8⁺ T cells, for example, rely on fatty acid oxidation for their long-term persistence. PPAR δ is reported to promote the switch from glycolysis to oxidative metabolism during the formation of memory T cells. It can suppress anaerobic glycolysis in activated T cells, thereby favoring a metabolic state that is less inflammatory and more conducive to longevity and immune regulation.^{67,68} In CD, where a chronic inflammatory environment may skew T cells towards continuous effector activity (and thus glycolytic metabolism), PPAR δ activation might push some of these cells toward a memory or regulatory phenotype by altering their metabolic programming. Additionally, PPAR δ in mesenchymal stem/stromal cells has been linked to the regulation of Th17 responses via metabolic effect⁶⁹ though this is an emerging area of study.

4. Therapeutic and Cautionary Notes

Unlike PPAR α and PPAR γ , no PPAR δ -targeted therapy is currently in use for IBD. In fact, full agonists of PPAR δ (like GW

501516) have raised concerns after causing tumors in rodent studies, halting their clinical development for metabolic diseases. PPAR δ 's pro-proliferative effects in certain contexts (e.g., promoting angiogenesis and cell survival in colorectal cancer models) warrant caution.⁷⁰ CD patients already carry an elevated risk of colorectal cancer due to chronic inflammation, so any intervention that broadly activates PPAR δ would need careful evaluation for cancer risk. On the other hand, selective modulation of PPAR δ in immune or Paneth cells might be beneficial. For instance, strategies to boost PPAR δ in the intestinal epithelium (without systemic exposure) could enhance barrier defense against bacteria without significant oncogenic risk. An interesting development in another field is the drug seladelpar, a PPAR δ agonist tested in primary biliary cholangitis, which appeared safe and effective in phase III trials (no cancers observed over a limited period).⁷¹ This suggests that with proper targeting and dosing, PPAR δ agonism might be harnessed therapeutically. Any such approach in CD would require ensuring that benefits (e.g., restoring Paneth cell function, reducing inflammation) outweigh potential long-term risks.

5. Summary

In summary, PPAR β/δ occupies a unique niche in intestinal homeostasis: it influences macrophage activation, supports Paneth cell-dependent microbial balance, and adjusts T cell metabolism. Its role in CD is less well defined than PPAR α/γ , but emerging evidence indicates that a deficiency in PPAR δ activity could contribute to microbial dysbiosis and perhaps sustained inflammation in CD patients. More research is needed to clarify whether PPAR δ could be a safe therapeutic target or biomarker in IBD. For the remainder of this review, our focus will return to the more immediately translational aspects of PPAR α and PPAR γ in CD, particularly how we can leverage these pathways for treatment.

CROSSTALK WITH MICROBIOTA, ADIPOSE TISSUE, AND VIRUSES IN PPAR SIGNALING

The activity of PPAR pathways in CD is not only determined by host genetics and cells-intrinsic factors, but also by external and microenvironmental influences. Gut microbes, mesenteric adipose tissue, and viral infections can all modulate PPAR signaling, thereby influencing disease outcomes.

1. Gut Microbiota and PPARs

The intestinal microbiota provides ligands and signals that

modulate PPAR activity. Beneficial commensal bacteria produce SCFA like acetate, propionate, and butyrate, which, as discussed, can activate PPAR γ in colonocytes and macrophages. By upregulating PPAR γ , these microbial metabolites help maintain an anti-inflammatory tone and reinforce the mucosal barrier.⁷² When dysbiosis occurs in CD (often a decrease in SCFA-producing *Clostridia* and an increase in pro-inflammatory pathobionts), the supply of these PPAR-activating metabolites dwindles. This may lead to reduced PPAR signaling and thereby less restraint on inflammation. On the flip side, certain microbial components drive inflammation that inhibits PPAR function. For example, bacterial lipopolysaccharide through TLR4 activation triggers pathways (MAPK, NF- κ B) that can phosphorylate or otherwise impair PPAR γ 's transcriptional activity.⁷³ In IBD patients, increased TLR4 signaling in active disease correlates with decreased PPAR γ expression in the colon.⁷⁴ There is also evidence of a direct microbiota-PPAR interface: PPAR α -deficient mice have an expansion of bacteria that incited colitis, whereas activating PPAR α leads to tolerance of microbiota and prevention of dysbiosis-driven inflammation.^{75,76} Intriguingly, some bacteria might actively exploit PPAR pathways; one report showed that Enterobacteriaceae (a family often overgrown in CD dysbiosis) can flourish if PPAR γ signaling in epithelial cells is suppressed, whereas robust epithelial PPAR γ activation can inhibit the bloom of these pro-inflammatory bacteria.⁷⁵ In summary, a healthy microbiome likely promotes PPAR activity (through metabolites and low-level tonic signals), and in turn PPARs help maintain a balanced microbiome—a positive feedback loop that, when broken, contributes to IBD.

2. Mesenteric Adipose Tissue (“Creeping Fat”)

CD uniquely features hypertrophy of mesenteric fat wrapping around the inflamed intestine. This creeping fat is not merely a side effect but actively participates in immune regulation. Adipocytes and stromal cells in creeping fat secrete a host of cytokines and adipokines: for instance, leptin (pro-inflammatory, promoting Th1 responses and fibrogenesis) is elevated in CD fat, whereas adiponectin (usually anti-inflammatory) may be dysregulated.^{77,78} PPAR γ is the master regulator of adipocyte differentiation and function; thus, it is highly relevant in creeping fat biology. In fact, single-cell RNA-seq has identified cell subsets in CD mesenteric fat with upregulated PPAR γ signaling, particularly in a subset of preadipocyte/stromal cells that co-express genes for lipid metabolism and antimicrobial defense.¹⁶ This suggests creeping fat might mount a PPAR γ -

driven response to help contain bacterial spread from the intestine (acting as an immunometabolic “firewall”). PPAR γ activation in adipose tissue tends to induce adiponectin and suppress leptin, skewing towards anti-inflammatory adipokine profiles. Consistently, thiazolidinedione PPAR γ agonists increase adiponectin levels systemically and could potentially do so in mesenteric fat, thereby mitigating local inflammation. Moreover, creeping fat produces PEA and other PPAR α ligands *in situ*,^{79,80} which may diffuse into the intestine and dampen inflammation. However, if PPAR signaling in creeping fat is insufficient or becomes aberrant, the fat may become a chronic source of inflammation and fibrosis. Leptin from PPAR γ -deficient adipocytes, for example, can drive macrophages toward collagen-producing, TNF-secreting phenotypes that exacerbate strictures.⁸¹ Therefore, maintaining normal PPAR function in mesenteric fat is likely important for its proposed “shielding” role in CD. This interplay is complex: creeping fat can be viewed as both a marker of severe CD and an effort by the body to localize disease; PPARs within that fat determine whether it is friend or foe to the intestine.

3. Viral Interactions

Viral infections have been proposed as environmental triggers or exacerbating factors for IBD. Certain viruses can modulate host PPAR pathways, thereby influencing inflammation. For example, influenza virus has been shown to deliberately downregulate PPAR γ in alveolar macrophages, causing an exaggerated inflammatory response (a “cytokine storm”).⁸² In that context, treating infected mice with a PPAR γ agonist blunted harmful inflammation without impairing viral clearance. While the lung is a different organ, similar principles may apply in the gut: a viral gastroenteritis could transiently suppress PPAR γ or PPAR α in intestinal immune cells, lowering the threshold for a CD flare. Notably, type I interferons produced during viral infection can inhibit PPAR α 's lipid metabolic genes (since interferon signaling shifts cell metabolism toward an antiviral state), which might curtail PPAR α 's anti-inflammatory effects during and after the infection. There is also evidence that some viral proteins interact with PPARs; for instance, human immunodeficiency virus type 1 (HIV-1) gp120 was found to influence PPAR γ activity in microglia, promoting inflammation.⁸³ In the gastrointestinal realm, norovirus is temporally linked to triggering flares in CD patients, especially those with genetic autophagy defects. It is conceivable that noroviral infection of intestinal immune cells could interfere with PPAR γ , compounding inflammation. On a more positive note, PPAR

agonists have shown antiviral benefits in some studies: PPAR γ activation can promote barrier integrity during viral infection of the gut. A striking example comes from simian immunodeficiency virus-infected macaques (a model of HIV gut pathology)—administration of a cannabinoid Tetrahydrocannabinol (THC), which engages PPAR γ , was found to improve intestinal epithelial integrity and reduce microbial translocation in the infected monkeys.⁸⁴ This suggests that enhancing PPAR γ during chronic viral infection protects the gut lining and limits immune activation. In summary, viruses can tip the balance of PPAR signaling to favor inflammation, and in such cases PPAR activation could serve as an adjunctive strategy to maintain remission in CD patients prone to viral reactivations.

4. Summary

In essence, PPAR pathways in CD are dynamically influenced by the microbial and viral milieu and by the metabolic signals from adjacent tissues like fat. Understanding these interactions is crucial because they may explain fluctuations in disease activity and responses to therapy. For instance, a patient's diet (affecting microbiota and metabolites) or intercurrent viral infections might change PPAR activity and thus the effectiveness of a PPAR-targeted treatment. It also opens the door to combination interventions—for example, using prebiotics or probiotics to boost PPAR agonist availability (such as butyrate producers) alongside pharmacologic PPAR activators. The complexity of these networks underscores that successful modulation of PPARs in CD may require a holistic approach, addressing not only the receptor and its ligands but also the environment that feeds into this signaling system.

THERAPEUTIC IMPLICATIONS: PPAR-TARGETED INTERVENTIONS IN CD

Given their significant roles in regulating inflammation and metabolism, PPARs have attracted considerable interest as therapeutic targets in IBD. Both synthetic ligands (drugs developed for other indications) and natural compounds that activate PPAR α or PPAR γ are being repurposed or optimized for IBD treatment. Synthetic agents like thiazolidinediones (pioglitazone, rosiglitazone, troglitazone) activate PPAR γ to reduce pro-inflammatory cytokines and NF- κ B signaling, with promising preclinical and early clinical data. PPAR α agonists (e.g., fibrates) and dual agonists enhance fatty acid oxidation and suppress inflammation but require careful use due to metabolic risks. Although PPAR δ agonists are not yet used

Table 2. The Current State of PPAR-Directed Therapies and Their Mechanisms of Action in the Context of Crohn's Disease

Therapy type	Compound	PPAR target	Experimental model	Effect
Synthetic	Pioglitazone	PPAR γ	DSS-induced colitis mice	Inhibits NF- κ B activation, reducing inflammation ⁸⁵
	Rosiglitazone	PPAR γ	HT-29, Caco-2 cells; DSS-colitis mice, rats	Inhibits IL-6, TNF- α , NF- κ B; reduces neutrophil chemotaxis ⁸⁶
	Troglitazone	PPAR γ	HT-29, Caco-2 cells; DSS-colitis mice	Inhibits NF- κ B activation, reducing inflammation ^{87,88}
	Adelmidrol	PPAR α , CB1, CB2	DNBS-induced colitis mice	Reduces NF- κ B translocation, COX2, MAPK, cytokines; modulates ICAM-1, etc ⁸⁹
	CBt-PMN	PPAR β/δ , RXR	DSS-induced colitis mice	Down-regulates TNF- α , IL-6 in monocytes ⁹⁰
	GW0742	PPAR β/δ	DSS-induced colitis mice	Reduces pro-inflammatory cytokines; improves histological scores ⁹¹
	Tropisetron	PPAR γ	DSS-induced colitis mice	Reduces pro-inflammatory cytokines; improves histological scores ⁹²
	GED-0507-34 Levo	PPAR γ	Mice, inflammation-driven fibrosis	Studied for anti-fibrotic effects ³³
	n3-PUFA (DHA, EPA)	PPAR γ , NFAT	TNBS-colitis rats	Decreases inflammation, IL-2, IL-4; increases PPAR γ ; reduces NFAT expression ⁹³
	Abelmoschus manihot extract	PPAR γ	DSS-colitis mice	Regulates gut microbiota and Th17/Treg balance ⁹⁴
Natural	Magnolol	PPAR γ	DSS-colitis mice	Counteracts TNF- α , IL-1 β , IL-12 via NF- κ B pathway regulation ⁹⁵
	Oxylipins (<i>Chlamydomonas debaryana</i>)	PPAR γ	TNBS-colitis mice	Decreases TNF- α , IL-1 β , IL-6, IL-17, COX2, NF- κ B; improves morphology ⁹⁶
	Portulaca oleracea extract	PPAR γ	DSS-colitis mice	Inhibits pro-inflammatory cytokine release, reduces NF- κ B phosphorylation ⁹⁷
	Sargahydroquinoidic acid	PPAR γ	HT-29, Caco-2 cells	Dual anti-inflammatory and antioxidant effects ⁹⁸
	Tetramethylpyrazine	PPAR γ	OXA-colitis mice, Caco-2 cells	Reduces TNF- α , IL-6, IL-8, ROS via PPAR γ signaling; inhibits NF- κ B ⁹⁹
	Verbascoside	PPAR α	Mice, IBD model	Activates PPAR α , reducing inflammation ¹⁰⁰
	Oleyethanolamide	PPAR α	DSS-colitis rats	Activates PPAR α , involved in feeding regulation and anti-inflammatory effects ¹⁰¹

PPAR, peroxisome proliferator-activated receptor; DSS, dextran sulfate sodium; NF- κ B, nuclear factor kappa B; IL, interleukin; TNF- α , tumor necrosis factor-alpha; DNBS, dinitrobenzene sulfonic acid; COX2, cyclooxygenase-2; MAPK, mitogen-activated protein kinase; ICAM-1, intercellular adhesion molecule 1; RXR, retinoid X receptor; NFAT, nuclear factor of activated T-cells; ROS, reactive oxygen species; OXA, oxazolone; IBD, Inflammatory bowel disease.

clinically due to safety concerns, indirect activation via exercise or partial modulators may offer future potential. Natural compounds—such as omega-3 fatty acids, curcumin, resveratrol, and fiber-derived butyrate—modulate PPAR activity and show anti-inflammatory and gut barrier-enhancing effects in models of colitis. Table 2 reviews the current state of PPAR-directed therapies and their mechanisms of action in the context of preclinical models of IBD such as DSS-induced colitis.^{33,85-101} It is important to note that DSS colitis is largely confined to the colon and causes superficial mucosal inflammation, whereas CD often features transmural inflammation,

patchy (“skip”) lesions, and frequent ileal involvement, which DSS does not replicate. Notably, DSS-induced inflammation is driven by epithelial injury and innate immune activation, with minimal adaptive (T-cell) priming, and granulomas or fistulas typical of CD pathology do not occur in DSS models. These differences mean that findings from DSS models may not fully translate to CD. For example, PPAR-targeted therapies that show efficacy in DSS colitis might behave differently in a CD-like immune milieu. Indeed, the same PPAR agonist can yield opposite outcomes in different models: fenofibrate (a PPAR α agonist) improved chronic Th1-driven colitis in IL-

10 knockout mice (a CD-like model) but actually exacerbated acute DSS colitis via altered lipid metabolism and necrosis pathways.^{60,61} This underscores while DSS studies provide valuable insights, their relevance to CD must be viewed with caution, given the stark pathophysiological differences.

1. Mechanistic Considerations and Personalized Therapy

The therapeutic exploitation of PPARs in CD raises the question of patient selection and personalization. Not all patients may equally benefit from PPAR modulation. Potential factors to consider:

- **PPAR expression and activation status:** Some patients, especially those with long-standing inflammation, might have profoundly low PPAR γ expression in their intestinal tissue (as seen in subsets of IBD patients).³⁹ These individuals could be ideal candidates for PPAR γ augmentation therapy, since their baseline anti-inflammatory checks are blunted. On the other hand, patients whose disease is primarily driven by pathways unrelated to PPAR (e.g., IL-23/Th17 axis overwhelming everything) might not respond as well to PPAR agonists. Molecular profiling of a biopsy – looking at PPAR α/γ target gene expression – could serve as a biomarker of an ongoing PPAR activity. Low PPAR target gene signature might predict a more robust response to a PPAR agonist (because there is more “room” to activate those pathways).
- **Genetic polymorphisms:** PPAR γ Pro12Ala polymorphism and possibly other variants could influence individual responses.⁴¹ While Pro12Ala is not common in CD, if present it results in a less active PPAR γ . Paradoxically, one might think patients with this variant would respond even better to PPAR γ agonists (as pharmacologic activation might compensate for genetic hypofunction). Conversely, those with inherently hyperactive PPAR variants might not need additional activation. Beyond PPAR genes themselves, polymorphisms in PPAR co-regulators (like PGC1 α , or co-repressor genes) or upstream signals (like fatty acid binding proteins that deliver ligands to PPAR) could also modulate efficacy. As pharmacogenomic research in IBD advances, we may identify a panel of gene markers that predict who will benefit from PPAR-targeted therapy.
- **Disease location and behavior:** It is conceivable that colonic-predominant CD might respond differently to PPAR γ agonists than small-bowel CD. PPAR γ is more highly expressed in the colon, and agents like 5-ASA (a PPAR γ acti-

vator) work in UC (a colonic disease) but not reliably in small-bowel CD. For small intestine disease, PPAR α (abundant in ileal enterocytes and liver) might be more relevant – for example, patients with fistulizing ileal CD might benefit from PPAR α -driven improvements in barrier function and bacterial clearance. Likewise, a fibrostenosing phenotype might particularly merit PPAR γ therapy for its anti-fibrotic effects, whereas an inflammatory phenotype might benefit from both PPAR α and PPAR γ activation to quell inflammation.

- **Microbiome composition:** The baseline microbiota might also guide therapy. A patient whose microbiome is rich in butyrate producers (indicating good natural PPAR γ ligand availability) might not need as much PPAR γ agonist drug, whereas someone with a dysbiotic, SCFA-depleted microbiome might be a candidate for intensive PPAR γ activation (and possibly simultaneous microbiota restoration). There is an intriguing possibility of using microbiome metabolites as surrogate markers for PPAR engagement: e.g., measuring fecal SCFA or lipid mediator levels could reflect how robustly PPAR pathways are being stimulated in the gut.

Looking ahead, a personalized medicine approach for CD could involve stratifying patients by such biomarkers and tailoring a regimen that includes PPAR modulators. For instance, a young adult patient with moderate colonic CD, low PPAR γ expression on biopsy, and creeping fat seen on magnetic resonance imaging (suggesting active adipose involvement) might receive a PPAR γ agonist plus dietary supplementation (like curcumin and omega-3), on top of standard immune-suppressive therapy, aiming for both inflammation control and fibrosis prevention. On the other hand, an older patient with primarily ileal disease and a history of cardiovascular disease risk (where thiazolidinediones are relatively contraindicated) might be directed more towards a PPAR α -focused intervention (like a trial of fenofibrate, given its dual benefit on lipids and inflammation) if appropriate.

2. Translating PPAR Agonist Benefits from Cholestatic Liver Diseases to CD

The successful application of PPAR agonists in cholestatic liver diseases provides a compelling rationale for exploring their use in CD. The anti-inflammatory and anti-fibrotic properties of PPAR α and PPAR γ agonists observed in cholestatic liver diseases could similarly attenuate intestinal inflammation and fibrosis in CD.^{102,103}

Moreover, the interplay between mesenteric adipose tissue

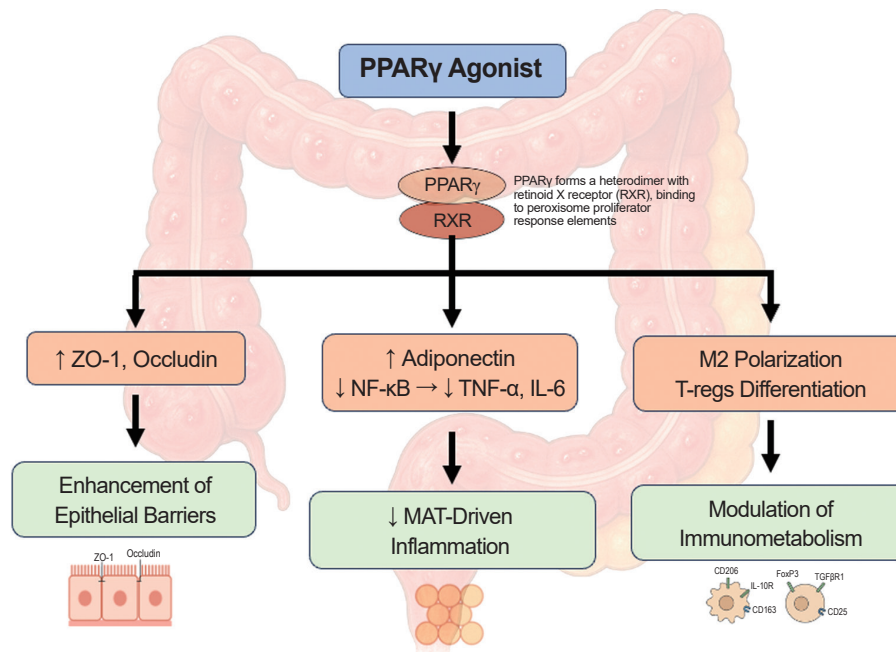


Fig. 1. Schematic representation of the proposed anti-inflammatory and barrier-enhancing effects of peroxisome proliferator-activated receptor (PPAR) γ agonism in the gut. Upon activation, PPAR γ forms a heterodimer with retinoid X receptor (RXR), binding to peroxisome proliferator response elements and initiating transcriptional programs that (1) upregulate tight junction proteins ZO-1 and occludin, enhancing epithelial barrier integrity; (2) increase adiponectin and suppress nuclear factor kappa B (NF- κ B) signaling, leading to reduced pro-inflammatory cytokines tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6) in mesenteric adipose tissue (MAT); and (3) promote M2 macrophage polarization and regulatory T cell (Treg) differentiation, thereby modulating immunometabolism. Most of the evidence supporting these mechanisms is derived from preclinical models and should be interpreted with caution in the context of human inflammatory bowel disease.

and intestinal inflammation in CD parallels the role of adipose tissue in primary biliary cholangitis and primary sclerosing cholangitis, where PPAR agonists regulate adipokine secretion and inflammatory responses.¹⁰³ Additionally, the safety and tolerability of PPAR agonists as shown in studies on cholestatic liver diseases support its potential trial in CD.^{104,105} However, despite the promising short-term biochemical responses observed with newer selective PPAR agonists like elafibranor and seladelpar, long-term efficacy and safety profiles remain areas requiring further investigation.¹⁰⁶

Most PPAR agonists share lipid-binding moieties that facilitate receptor dimerization and anti-NF- κ B activity. Future studies should prioritize: (1) comparative trials of PPAR α vs PPAR γ agonists in CD; (2) pharmacogenomic profiling of PPAR variants; and (3) microbiota-targeted approaches to modulate endogenous PPAR ligands.

FUTURE PERSPECTIVES

Research over the past decade has solidified that PPAR α and

PPAR γ are integral regulators of the immunometabolic disturbances in CD. They function at the intersection of metabolic and inflammatory signaling—a nexus highly relevant to a disease characterized by chronic immune activation amid environmental and dietary challenges. PPARs help govern the balance between pro- and anti-inflammatory immune cells, maintain the integrity of the gut barrier, influence the microbial ecosystem, and even modulate fibrogenesis (Fig. 1). In CD, these receptors often appear underactive or overwhelmed, evidenced by reduced expression in active disease and the exaggerated inflammation seen in PPAR-deficient models.¹¹ Harnessing PPAR pathways thus represents a compelling strategy to restore homeostasis.

Therapeutically, there is now a clearer path forward for PPAR-targeted approaches in IBD. Clinical trials of PPAR γ agonists, while still few, demonstrate proof-of-concept that enhancing PPAR signaling can translate into clinical improvement (as shown in UC and suggested in pilot CD studies). The ongoing development of gut-specific PPAR modulators (like MBF-118) and the exploration of dual agonists or combination

treatments provide optimism that efficacy can be achieved without undue side effects. Likewise, repurposing safe existing medications (e.g., fibrates, which have decades of clinical use in metabolic diseases) for adjunct IBD therapy is an attractive low-cost avenue. Even if PPAR agonists by themselves are not sufficient to induce remission in severe CD, they could be combined with immune biologics to address aspects those biologics do not—for example, using a PPAR γ agonist alongside an anti-TNF agent might synergistically reduce inflammation and at the same time promote mucosal healing and reduce fibrosis, ultimately improving long-term outcomes.

Moreover, the interplay between gut microbiota and PPARs opens new therapeutic concepts: fostering a microbiome that naturally activates PPARs could be a gentle way to keep inflammation at bay. This might involve diet plans or next-generation probiotics engineered to secrete PPAR-activating metabolites in the intestine. Similarly, understanding PPARs' role in mesenteric fat may inspire therapies aimed at “reprogramming” creeping fat from a pro-inflammatory tissue to a healing one—perhaps by local PPAR γ stimulation to increase anti-inflammatory adipokine release.

Of course, challenges remain. Much of the current mechanistic understanding of PPAR signaling in IBD is derived from *in vitro* models and animal studies, and thus, its translational relevance to human disease must be interpreted with caution and validated in robust clinical trials. Additionally, PPAR-targeted drugs must be fine-tuned to avoid unwanted systemic effects. Long-term safety data in the context of IBD (where patients may be young and on therapy for life) will be needed. Also, CD is heterogeneous; PPAR modulation may dramatically help some patients but be less effective in others, so identifying predictors of response is crucial. As we accumulate more clinical trial data and real-world experiences, these questions will be answered.

In conclusion, the role of PPARs in CD exemplifies the growing realization that metabolic pathways are inseparable from immune regulation in chronic inflammatory disorders. PPAR α and PPAR γ act as guardians of gut immune homeostasis by sensing metabolic cues and appropriately tuning immune and epithelial cell function. Their impairment can tip the scales toward uncontrolled inflammation, whereas their activation can restore equilibrium. With an armamentarium of PPAR agonists (both old and new) at our disposal, gastroenterology stands at the cusp of translating these insights into novel therapies. The coming years will likely see PPAR-focused treatment strategies moving from bench to bedside—poten-

tially inaugurating a new era of immunometabolic therapy for CD, wherein nurturing the body's own regulatory pathways leads to deeper and more durable remission for patients. Such an approach, especially if personalized, holds promise to tackle facets of CD that remain difficult to manage with current therapies, bringing us closer to the goal of complete mucosal healing and disease modification in CD.

ADDITIONAL INFORMATION

Funding Source

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability Statement

Not applicable.

Author Contributions

Conceptualization: Bashiri K. Supervision: Mattar MC, Meighani A, Mason AL. Visualization: Bashiri K. Writing - original draft: Bashiri K. Writing - review & editing: Mattar MC, Meighani A, Mason AL. Approval of final manuscript: all authors.

Additional Contributions

The authors thank the Center of Excellence for Gastrointestinal Inflammation and Immunity Research at the University of Alberta for providing critical feedback and resources for this study.

ORCID

Bashiri K	https://orcid.org/0000-0003-4359-9925
Mattar MC	https://orcid.org/0000-0002-9339-1607
Meighani A	https://orcid.org/0000-0002-0990-2647
Mason AL	https://orcid.org/0000-0002-0470-9522

REFERENCES

1. Dolinger M, Torres J, Vermeire S. Crohn's disease. *Lancet* 2024; 403:1177-1191.
2. Decara J, Rivera P, López-Gamero AJ, et al. Peroxisome proliferator-activated receptors: experimental targeting for the treatment of inflammatory bowel diseases. *Front Pharmacol*

- 2020;11:730.
3. Katkar GD, Sayed IM, Anandachar MS, et al. Artificial intelligence-rationalized balanced PPAR α / γ dual agonism resets dysregulated macrophage processes in inflammatory bowel disease. *Commun Biol* 2022;5:231.
4. Sato-Espinoza K, Chotiprasidhi P, Huaman MR, Díaz-Ferrer J. Update in lean metabolic dysfunction-associated steatotic liver disease. *World J Hepatol* 2024;16:452-464.
5. Caioni G, Viscido A, d'Angelo M, et al. Inflammatory bowel disease: new insights into the interplay between environmental factors and PPAR γ . *Int J Mol Sci* 2021;22:985.
6. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism* 2021;114:154338.
7. Pan X, Zhu Q, Pan LL, Sun J. Macrophage immunometabolism in inflammatory bowel diseases: from pathogenesis to therapy. *Pharmacol Ther* 2022;238:108176.
8. Wagner N, Wagner KD. The role of PPARs in disease. *Cells* 2020;9:2367.
9. Wang YX, Zhang CL, Yu RT, et al. Regulation of muscle fiber type and running endurance by PPAR δ . *PLoS Biol* 2004;2:e294.
10. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med* 2024;390:783-794.
11. Posta E, Fekete I, Varkonyi I, Zold E, Barta Z. The versatile role of peroxisome proliferator-activated receptors in immune-mediated intestinal diseases. *Cells* 2024;13:1688.
12. Iftikhar QU, Iftikhar MK, Iqbal J, Sathian B. Balancing promise and uncertainty: PPAR agonists in IBD therapy. *J Gastroenterol Hepatol* 2025;40:1646-1647.
13. Di Y, Li H, Yang J, et al. PPAR γ /NF- κ B axis contributes to cold-induced resolution of experimental colitis and preservation of intestinal barrier. *Biochim Biophys Acta Mol Basis Dis* 2024;1870:167326.
14. Kim IS, Silwal P, Jo EK. Peroxisome proliferator-activated receptor-targeted therapies: challenges upon infectious diseases. *Cells* 2023;12:650.
15. Shu W, Wang Y, Li C, et al. Single-cell expression atlas reveals cell heterogeneity in the creeping fat of Crohn's disease. *Inflamm Bowel Dis* 2023;29:850-865.
16. Aggeletopoulou I, Tsounis EP, Mouzaki A, Triantos C. Creeping fat in Crohn's disease: surgical, histological, and radiological approaches. *J Pers Med* 2023;13:1029.
17. Manoharan I, Suryawanshi A, Hong Y, et al. Homeostatic PPAR α signaling limits inflammatory responses to commensal microbiota in the intestine. *J Immunol* 2016;196:4739-4749.
18. Feng T, Qin H, Wang L, Benveniste EN, Elson CO, Cong Y. Th17 cells induce colitis and promote Th1 cell responses through IL-17 induction of innate IL-12 and IL-23 production. *J Immunol* 2011;186:6313-6318.
19. Kanakasabai S, Walline CC, Chakraborty S, Bright JJ. PPAR δ deficient mice develop elevated Th1/Th17 responses and prolonged experimental autoimmune encephalomyelitis. *Brain Res* 2011;1376:101-112.
20. Bach Knudsen KE, Lærke HN, Hedemann MS, et al. Impact of diet-modulated butyrate production on intestinal barrier function and inflammation. *Nutrients* 2018;10:1499.
21. Beamer BA, Negri C, Yen CJ, et al. Chromosomal localization and partial genomic structure of the human peroxisome proliferator activated receptor-gamma (hPPAR gamma) gene. *Biochem Biophys Res Commun* 1997;233:756-759.
22. Vetuschi A, Pompili S, Gaudio E, Latella G, Sferra R. PPAR- γ with its anti-inflammatory and anti-fibrotic action could be an effective therapeutic target in IBD. *Eur Rev Med Pharmacol Sci* 2018;22:8839-8848.
23. Klepsch V, Moschen AR, Tilg H, Baier G, Hermann-Kleiter N. Nuclear receptors regulate intestinal inflammation in the context of IBD. *Front Immunol* 2019;10:1070.
24. Hontecillas R, Horne WT, Climent M, et al. Immunoregulatory mechanisms of macrophage PPAR- γ in mice with experimental inflammatory bowel disease. *Mucosal Immunol* 2011;4:304-313.
25. Kristek M. Crosstalk between epithelial cells and macrophages in the gut: the role of TNFR2 [PhD thesis]. Dublin: Dublin City University, 2014.
26. Guri AJ, Mohapatra SK, Horne WT, Hontecillas R, Bassaganya-Riera J. The role of T cell PPAR gamma in mice with experimental inflammatory bowel disease. *BMC Gastroenterol* 2010;10:60.
27. Saubermann LJ, Nakajima A, Wada K, et al. Peroxisome proliferator-activated receptor gamma agonist ligands stimulate a Th2 cytokine response and prevent acute colitis. *Inflamm Bowel Dis* 2002;8:330-339.
28. Mohapatra SK, Guri AJ, Climent M, et al. Immunoregulatory actions of epithelial cell PPAR gamma at the colonic mucosa of mice with experimental inflammatory bowel disease. *PLoS One* 2010;5:e10215.
29. Adachi M, Kurotani R, Morimura K, et al. Peroxisome proliferator activated receptor gamma in colonic epithelial cells protects against experimental inflammatory bowel disease. *Gut* 2006;55:1104-1113.

30. Koo JB, Nam MO, Jung Y, et al. Anti-fibrogenic effect of PPAR- γ agonists in human intestinal myofibroblasts. *BMC Gastroenterol* 2017;17:73.
31. Ghosh AK, Bhattacharyya S, Wei J, et al. Peroxisome proliferator-activated receptor-gamma abrogates Smad-dependent collagen stimulation by targeting the p300 transcriptional coactivator. *FASEB J* 2009;23:2968-2977.
32. McVicker BL, Bennett RG. Novel anti-fibrotic therapies. *Front Pharmacol* 2017;8:318.
33. Specia S, Rousseaux C, Dubuquoy C, et al. Novel PPAR γ modulator GED-0507-34 levo ameliorates inflammation-driven intestinal fibrosis. *Inflamm Bowel Dis* 2016;22:279-292.
34. Cominelli F, Arseneau KO, Rodriguez-Palacios A, Pizarro TT. Uncovering pathogenic mechanisms of inflammatory bowel disease using mouse models of Crohn's disease-like ileitis: what is the right model? *Cell Mol Gastroenterol Hepatol* 2017;4:19-32.
35. Rousseaux C, El-Jamal N, Fumery M, et al. The 5-aminosalicylic acid antineoplastic effect in the intestine is mediated by PPAR γ . *Carcinogenesis* 2013;34:2580-2586.
36. Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med* 2005;201:1205-1215.
37. Dubuquoy L, Jansson EA, Deeb S, et al. Impaired expression of peroxisome proliferator-activated receptor gamma in ulcerative colitis. *Gastroenterology* 2003;124:1265-1276.
38. Yamamoto-Furusho JK, Peñaloza-Coronel A, Sánchez-Muñoz F, Barreto-Zuñiga R, Dominguez-Lopez A. Peroxisome proliferator-activated receptor-gamma (PPAR- γ) expression is downregulated in patients with active ulcerative colitis. *Inflamm Bowel Dis* 2011;17:680-681.
39. Dou X, Xiao J, Jin Z, Zheng P. Peroxisome proliferator-activated receptor- γ is downregulated in ulcerative colitis and is involved in experimental colitis-associated neoplasia. *Oncol Lett* 2015;10:1259-1266.
40. Liu C, Jiang Y, Liu G, et al. PPARGC1A affects inflammatory responses in photodynamic therapy (PDT)-treated inflammatory bowel disease (IBD). *Biochem Pharmacol* 2022;202:115119.
41. Zhang ZF, Yang N, Zhao G, Zhu L, Wang LX. Association between the Pro12Ala polymorphism of peroxisome proliferator-activated receptor gamma 2 and inflammatory bowel disease: a meta-analysis. *PLoS One* 2012;7:e30551.
42. Atug O, Tahan V, Eren F, et al. Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) gene in inflammatory bowel disease. *J Gastrointest Liver Dis* 2008;17:433-437.
43. Mandard S, Patsouris D. Nuclear control of the inflammatory response in mammals by peroxisome proliferator-activated receptors. *PPAR Res* 2013;2013:613864.
44. Tahri-Joutey M, Andreoletti P, Surapureddi S, Nasser B, Cherkaoui-Malki M, Latruffe N. Mechanisms mediating the regulation of peroxisomal fatty acid beta-oxidation by PPAR α . *Int J Mol Sci* 2021;22:8969.
45. Grabacka M, Plonka PM, Pierzchalska M. The PPAR α regulation of the gut physiology in regard to interaction with microbiota, intestinal immunity, metabolism, and permeability. *Int J Mol Sci* 2022;23:14156.
46. Grabacka M, Pierzchalska M, Plonka PM, Pierzchalski P. The role of PPAR alpha in the modulation of innate immunity. *Int J Mol Sci* 2021;22:10545.
47. Lama A, Provensi G, Amoriello R, et al. The anti-inflammatory and immune-modulatory effects of OEA limit DSS-induced colitis in mice. *Biomed Pharmacother* 2020;129:110368.
48. Korbecki J, Bobiński R, Dutka M. Self-regulation of the inflammatory response by peroxisome proliferator-activated receptors. *Inflamm Res* 2019;68:443-458.
49. Guo Q, Jin Y, Chen X, et al. NF- κ B in biology and targeted therapy: new insights and translational implications. *Signal Transduct Target Ther* 2024;9:53.
50. Ricote M, Glass CK. PPARs and molecular mechanisms of transrepression. *Biochim Biophys Acta* 2007;1771:926-935.
51. Gelfand EW. Importance of the leukotriene B₄-BLT1 and LTB₄-BLT2 pathways in asthma. *Semin Immunol* 2017;33:44-51.
52. Bougarne N, Weyers B, Desmet SJ, et al. Molecular actions of PPAR α in lipid metabolism and inflammation. *Endocr Rev* 2018;39:760-802.
53. Liébana-García R, Olivares M, Francés-Cuesta C, et al. Intestinal group 1 innate lymphoid cells drive macrophage-induced inflammation and endocrine defects in obesity and promote insulinemia. *Gut Microbes* 2023;15:2181928.
54. Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: a natural compound for health management. *Int J Mol Sci* 2021;22:5305.
55. Borrelli F, Romano B, Petrosino S, et al. Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. *Br J Pharmacol* 2015;172:142-158.
56. Lo Verme J, Fu J, Astarita G, et al. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-

- inflammatory actions of palmitoylethanolamide. *Mol Pharmacol* 2005;67:15-19.
57. Sá MCI, Castor MGM. Therapeutic use of palmitoylethanolamide as an anti-inflammatory and immunomodulator. *Future Pharmacol* 2023;3:951-977.
58. Basso PJ, Sales-Campos H, Nardini V, et al. Peroxisome proliferator-activated receptor alpha mediates the beneficial effects of atorvastatin in experimental colitis. *Front Immunol* 2021;12:618365.
59. Khalili H, Forss A, Söderling J, et al. Statin use is associated with a less severe disease course in inflammatory bowel disease: a nationwide cohort study 2006-2020. *Inflamm Bowel Dis* 2025;31:2787-2797.
60. Lee JW, Bajwa PJ, Carson MJ, et al. Fenofibrate represses interleukin-17 and interferon-gamma expression and improves colitis in interleukin-10-deficient mice. *Gastroenterology* 2007;133:108-123.
61. Qi Y, Jiang C, Tanaka N, et al. PPAR α -dependent exacerbation of experimental colitis by the hypolipidemic drug fenofibrate. *Am J Physiol Gastrointest Liver Physiol* 2014;307:G564-G573.
62. Alarfaj SJ, Bahaa MM, Elmasry TA, et al. Fenofibrate as an adjunct therapy for ulcerative colitis: targeting inflammation via SIRT1, NLRP3, and AMPK pathways: a randomized controlled pilot study. *Drug Des Devel Ther* 2024;18:5239-5253.
63. Liu Y, Colby JK, Zuo X, Jaoude J, Wei D, Shureiqi I. The role of PPAR- δ in metabolism, inflammation, and cancer: many characters of a critical transcription factor. *Int J Mol Sci* 2018;19:3339.
64. Geng T, Yan Y, Xu L, et al. CD137 signaling induces macrophage M2 polarization in atherosclerosis through STAT6/PPAR δ pathway. *Cell Signal* 2020;72:109628.
65. Varnat F, Heggeler BB, Grisel P, et al. PPARbeta/delta regulates paneth cell differentiation via controlling the hedgehog signaling pathway. *Gastroenterology* 2006;131:538-553.
66. Wallaey C, Garcia-Gonzalez N, Libert C. Paneth cells as the cornerstones of intestinal and organismal health: a primer. *EMBO Mol Med* 2023;15:e16427.
67. Bevilacqua A, Franco F, Lu YT, et al. PPAR β / δ -orchestrated metabolic reprogramming supports the formation and maintenance of memory CD8 T cells. *Sci Immunol* 2024;9:eadn 2717.
68. Shi Y, Zhang H, Miao C. Metabolic reprogram and T cell differentiation in inflammation: current evidence and future perspectives. *Cell Death Discov* 2025;11:123.
69. Contreras-Lopez RA, Elizondo-Vega R, Torres MJ, et al. PPAR β / δ -dependent MSC metabolism determines their immunoregulatory properties. *Sci Rep* 2020;10:11423.
70. Wang C, Lv T, Jin B, Li Y, Fan Z. Regulatory role of PPAR in colorectal cancer. *Cell Death Discov* 2025;11:28.
71. Hirschfield GM, Shiffman ML, Gulamhusein A, et al. Seladelpar efficacy and safety at 3 months in patients with primary biliary cholangitis: ENHANCE, a phase 3, randomized, placebo-controlled study. *Hepatology* 2023;78:397-415.
72. Wang J, Zhu N, Su X, Gao Y, Yang R. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. *Cells* 2023;12:793.
73. Wei J, Zhang Y, Li H, Wang F, Yao S. Toll-like receptor 4: a potential therapeutic target for multiple human diseases. *Biomed Pharmacother* 2023;166:115338.
74. Lu Y, Li X, Liu S, Zhang Y, Zhang D. Toll-like receptors and inflammatory bowel disease. *Front Immunol* 2018;9:72.
75. Byndloss MX, Olsan EE, Rivera-Chávez F, et al. Microbiota-activated PPAR- γ signaling inhibits dysbiotic Enterobacteriaceae expansion. *Science* 2017;357:570-575.
76. Hasan AU, Rahman A, Kobori H. Interactions between host PPARs and gut microbiota in health and disease. *Int J Mol Sci* 2019;20:387.
77. Tsounis EP, Aggeletopoulou I, Mouzaki A, Triantos C. Creeping fat in the pathogenesis of Crohn's disease: an orchestrator or a silent bystander? *Inflamm Bowel Dis* 2023;29:1826-1836.
78. Yin Y, Xie Y, Ge W, Li Y. Creeping fat formation and interaction with intestinal disease in Crohn's disease. *United European Gastroenterol J* 2022;10:1077-1084.
79. Gonthier MP, Hoareau L, Festy F, et al. Identification of endocannabinoids and related compounds in human fat cells. *Obesity (Silver Spring)* 2007;15:837-845.
80. Batacan R, Briskey D, Bajagai YS, Smith C, Stanley D, Rao A. Effect of palmitoylethanolamide compared to a placebo on the gut microbiome and biochemistry in an overweight adult population: a randomised, placebo controlled, double-blind study. *Biomedicines* 2024;12:1620.
81. Mao R, Kurada S, Gordon IO, et al. The mesenteric fat and intestinal muscle interface: creeping fat influencing stricture formation in Crohn's disease. *Inflamm Bowel Dis* 2019;25:421-426.
82. Zhang H, Alford T, Liu S, Zhou D, Wang J. Influenza virus causes lung immunopathology through down-regulating PPAR γ activity in macrophages. *Front Immunol* 2022;13:958801.
83. Omeragic A, Hoque MT, Choi UY, Bendayan R. Peroxisome proliferator-activated receptor-gamma: potential molecular therapeutic target for HIV-1-associated brain inflammation. *J*

- Neuroinflammation 2017;14:183.
84. Kumar V, Mansfield J, Fan R, MacLean A, Li J, Mohan M. miR-130a and miR-212 disrupt the intestinal epithelial barrier through modulation of PPAR γ and occludin expression in chronic simian immunodeficiency virus-infected rhesus macaques. *J Immunol* 2018;200:2677-2689.
85. Takagi T, Naito Y, Tomatsuri N, et al. Pioglitazone, a PPAR-gamma ligand, provides protection from dextran sulfate sodium-induced colitis in mice in association with inhibition of the NF-kappaB-cytokine cascade. *Redox Rep* 2002;7:283-289.
86. Sánchez-Hidalgo M, Martín AR, Villegas I, Alarcón De La Lastra C. Rosiglitazone, an agonist of peroxisome proliferator-activated receptor gamma, reduces chronic colonic inflammation in rats. *Biochem Pharmacol* 2005;69:1733-1744.
87. Kohno H, Yoshitani S, Takashima S, et al. Troglitazone, a ligand for peroxisome proliferator-activated receptor gamma, inhibits chemically-induced aberrant crypt foci in rats. *Jpn J Cancer Res* 2001;92:396-403.
88. Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K. Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. *Biochim Biophys Acta* 2004;1675:113-119.
89. Del Re A, Palenca I, Seguela L, et al. Oral adelmidrol administration up-regulates palmitoylethanolamide production in mice colon and duodenum through a PPAR- γ independent action. *Metabolites* 2022;12:457.
90. Onuki M, Watanabe M, Ishihara N, et al. A partial agonist for retinoid X receptor mitigates experimental colitis. *Int Immunol* 2019;31:251-262.
91. Li JH, Xu J, Hu JX, et al. PPAR γ / β/δ agonists can ameliorate dextran sodium sulfate-induced colitis and modulate gut microbiota. *J Gastroenterol Hepatol* 2025;40:1536-1547.
92. Motavallian A, Minaiyan M, Rabbani M, Andalib S, Mahzouni P. Involvement of 5HT₃ receptors in anti-inflammatory effects of tropisetron on experimental TNBS-induced colitis in rat. *Bioimpacts* 2013;3:169-176.
93. Charpentier C, Chan R, Salameh E, et al. Dietary n-3 PUFA may attenuate experimental colitis. *Mediators Inflamm* 2018; 2018:8430614.
94. Zhang W, Cheng C, Han Q, et al. Flos Abelmoschus manihot extract attenuates DSS-induced colitis by regulating gut microbiota and Th17/Treg balance. *Biomed Pharmacother* 2019;117:109162.
95. Shen P, Zhang Z, He Y, et al. Magnolol treatment attenuates dextran sulphate sodium-induced murine experimental colitis by regulating inflammation and mucosal damage. *Life Sci* 2018;196:69-76.
96. Ávila-Román J, Talero E, Rodríguez-Luna A, García-Mauriño S, Motilva V. Anti-inflammatory effects of an oxylipin-containing lyophilised biomass from a microalga in a murine recurrent colitis model. *Br J Nutr* 2016;116:2044-2052.
97. Kong R, Luo H, Wang N, et al. Extract attenuates development of dextran sulfate sodium induced colitis in mice through activation of PPAR. *PPAR Res* 2018;2018:6079101.
98. Nyambe MN, Koekemoer TC, van de Venter M, Goosen ED, Beukes DR. In vitro evaluation of the phytopharmacological potential of for the treatment of inflammatory bowel diseases. *Medicines (Basel)* 2019;6:49.
99. He X, Zheng Z, Yang X, Lu Y, Chen N, Chen W. Tetramethylpyrazine attenuates PPAR- γ antagonist-deteriorated oxazolone-induced colitis in mice. *Mol Med Rep* 2012;5:645-650.
100. Esposito E, Mazzon E, Paterniti I, et al. PPAR-alpha contributes to the anti-inflammatory activity of verbascoside in a model of inflammatory bowel disease in mice. *PPAR Res* 2010;2010:917312.
101. Otagiri S, Ohnishi S, Ohara M, et al. Oleoylethanolamide ameliorates dextran sulfate sodium-induced colitis in rats. *Front Pharmacol* 2020;11:1277.
102. Gallucci GM, Hayes CM, Boyer JL, Barbier O, Assis DN, Ghonem NS. PPAR-mediated bile acid glucuronidation: therapeutic targets for the treatment of cholestatic liver diseases. *Cells* 2024;13:1296.
103. Lemoine S, Pares A, Reig A, et al. Primary sclerosing cholangitis response to the combination of fibrates with ursodeoxycholic acid: French-Spanish experience. *Clin Res Hepatol Gastroenterol* 2018;42:521-528.
104. Floreani A, Gabbia D, De Martin S. Update on the pharmacological treatment of primary biliary cholangitis. *Biomedicines* 2022;10:2033.
105. Vuppalachchi R, Cruz MM, Momin T, et al. Pharmacokinetic, safety, and pharmacodynamic profiles of saroglitazar magnesium in cholestatic cirrhosis with hepatic impairment and participants with renal impairment. *Clin Pharmacol Ther* 2025;117:240-249.
106. Tanaka A, Corpechot C. PPAR agonists in PBC: where do we go from here? Or how to choose between the new and the old. *Clin Res Hepatol Gastroenterol* 2024;48:102358.