# **Pathophysiological Processes of IBD**

Subjects: Pathology Contributor: Elisabetta Benedetti

The pathophysiological processes of inflammatory bowel diseases (IBDs), i.e., Crohn's disease (CD) and ulcerative colitis (UC), are still not completely understood.

Keywords: PPARy ; pathophysiological processes of IBD ; environmental factors ; IBD models

### 1. Introduction

The worldwide epidemiology of inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (UC), has been influenced mainly by industrial progress and the improvement of human living conditions <sup>[1]</sup>. The increasing incidence and prevalence of IBD in developing countries suggest a connection with a westernized lifestyle and changed habits. The etiopathogenesis of IBD is not entirely understood. However, it is hypothesized to be related to a mixture of factors, including genetic susceptibility, dysregulation of the gut immune system, and environmental elements in conjunction with the microbiota. There is a need for complete information about these diseases since they represent an expanding global health problem, the costs of which are challenging to manage.

CD and UC are chronic inflammatory disorders with distinct clinical characteristics. CD can affect all gastrointestinal tract segments (most commonly the terminal ileum and colon) in a non-continuous manner, causing a typically asymmetrical, segmental, and transmural inflammation. CD complications include abscesses, fistulas, and strictures, and many patients need surgical procedures. UC involves the colonic mucosal surface, primarily affecting the rectum and, in some cases, the entire colon in a continuous manner. Depending on the extent of inflammation, UC can evolve into several forms, from proctitis to left-sides colitis or pancolitis <sup>[2]</sup>. Behind the different characteristics, CD and UC share almost common features regarding risk factors, symptoms, clinical course, complications, and the absence of a definitive cure. The current therapeutic approaches aim to reduce intestinal inflammation and, more specifically, block pro-inflammatory cytokines. However, the conventional therapy of IBD, i.e., salicylates, steroids, and immunosuppressants reduce the mortality, but not the rate of complications and surgery; the latter is required in up to 70% of CD and 20% of UC patients during their lifetime. The introduction of biological therapies, i.e., anti-tumor necrosis factor-alpha (TNF- $\alpha$ ), anti- $\alpha$ 4 $\beta$ 7 integrin, and anti-interleukins 12/23 antibodies, caused a revolution in the treatment of IBD; however, they reduced hospitalization, complications, and surgery only in the short- and medium-term. For these reasons, it is necessary to find personalized treatments employing new strategies for drug monitoring and, above all, identifying useful targets.

Concerning the underlying mechanism, IBD's pathogenesis seems to be related to an alteration in the innate immune system, including epithelial barrier defects with changes in E-cadherin,  $\beta$ -catenin, and claudins expression <sup>[3]</sup> and an inadequate expression of antimicrobial peptides. The gut immune homeostasis can be disrupted by innate immune cells contribution (neutrophils, dendritic cells, and macrophages) and the release of inflammatory mediators <sup>[4]</sup>. IBDs are typically characterized by high levels of cytokines, such as TNF- $\alpha$ , IL-6, IL-8 (one of the first chemokines described), IL-12, and chemokines such as chemokine ligand 2, chemokine ligand 3, and chemokine ligand 1 in colon tissues <sup>[5]</sup>. However, the role of adaptive immunity cannot be omitted since, in CD and UC patients, an alteration in immunoglobulin subclass production has been found <sup>[6]</sup>. Among other pathogenic components, there is an impairment in Peroxisome proliferator-activated receptors- $\gamma$  (PPAR $\gamma$ ) activity, abnormalities of the enteric nervous system, genetic variants, and the presence of regulatory RNAs <sup>[4]</sup>. The high expression of PPAR $\gamma$  in the bowel has already been demonstrated <sup>[7]</sup>, and several studies have shown its role in human colonic inflammation <sup>[8]</sup> along with the involvement of immune system response <sup>[9]</sup>. Notably, mesalazine, the most used drug in UC, binds and activates PPAR $\gamma$  <sup>[10]</sup>. Different xenobiotics and environmental pollutants can influence and alter the Peroxisome proliferator-activated receptors (PPAR) signaling pathway <sup>[11]</sup>. This evidence suggests a relationship between external factors and the onset of gut inflammation diseases.

## 2. PPARs: Crosstalk between Metabolism and Inflammation

PPARs are ligand-dependent transcription factors and belong to nuclear hormone receptors' superfamily, playing an important role in lipid and glucose metabolism <sup>[12]</sup>. In mammals, three isoforms of PPARs have been identified: PPAR $\alpha$  or NR1C1, PPAR $\beta/\delta$  or NR1C2, and PPAR $\gamma$  or NR1C, each of them encoded by a different gene. They share a similar structure. The ability to bind agonists is mediated by a ligand-binding domain (LBD) in the C-terminus, while the DNA binding domain is in the N-terminus. These receptors can be activated by natural fatty acids and eicosanoids or synthetic ligands, which are used in the clinical management of metabolic diseases, such as fibrates, with cardioprotective properties <sup>[13]</sup>, and thiazolidinediones, used in the treatment of diabetes mellitus type 2 <sup>[14]</sup>. After interaction with agonists, they are translocated in the nucleus, and their function depends on the heterodimerization with retinoid X receptor (RXR). The heterodimers bind to sequence-specific PPAR response elements (PPREs), stimulating the target genes' transcription <sup>[15]</sup>.

The members of the PPARs family show a wide range of actions on glucose and lipidic homeostasis, and they share many similarities in terms of structure and function; however, each isoform has a specific physiological activity, influenced by their tissue distribution.

PPAR $\alpha$  is expressed in tissues that require a large amount of energy, principally the liver, kidney, and skeletal muscle; its localization has also been demonstrated in cardiomyocytes, intestinal mucosa, adrenal gland, brown adipose tissue, and brain <sup>[16][17]</sup>. It is involved in the catabolism of fatty acids and their oxidation <sup>[18]</sup>. Regarding PPAR $\beta/\delta$ , this isoform is involved in several processes, including cell proliferation, differentiation, migration, and apoptosis. Its activity is also related to glucose and cholesterol homeostasis, insulin sensitivity, and angiogenesis <sup>[17][19]</sup>. It is ubiquitously expressed but particularly abundant in the gastrointestinal tract, kidneys, skeletal muscle, and brain <sup>[20]</sup>. PPAR $\gamma$  is abundantly expressed in white and brown adipose tissue, where it plays a crucial role in regulating adipogenesis, energy balance, and lipid biosynthesis. It is also expressed in the intestines, liver, kidneys, brain, immunological system, and muscles <sup>[17]</sup>.

PPARs are usually described as the main actors in lipid and glucose metabolism, but much evidence indicates their involvement in controlling inflammatory responses and inflammation-related disorders such as fibrosis and cancer. In addition to their known anti-inflammatory action, PPARs also modulate fibrogenesis and carcinogenesis.

It has been reported that PPARs have anti-inflammatory potential, modulating several points of inflammatory pathways. Inflammation consists of a dynamic sequence of phenomena, including the release of mediators that leads to vasodilatation, increased blood flow, vascular permeability, and recruitment of polymorphonuclear cells, particularly neutrophils in acute phase of inflammatory process, whereas mononuclear cells, macrophages, T- and B-lymphocytes are in chronic immunomediated inflammation. PPARs could intervene at each level of these processes. For example, PPAR $\alpha$  can negatively interfere with the NF-kB signaling pathway, repressing several inflammatory genes such as VCAM-1, COX-2, and IL-6 <sup>[22]</sup>. PPAR $\alpha$  is also involved in inhibiting the expression of inducible nitric oxide synthase <sup>[23]</sup> and TNF- $\alpha$  in macrophages <sup>[24]</sup>. PPAR $\beta$ / $\delta$  activity is induced in the host inflammatory response in the skin, and it results in being up-regulated in keratinocytes as a consequence of external triggers. The activation of PPAR- $\beta$ / $\delta$ -pathway determines the expression of genes related to keratinocyte differentiation, survival, and repair <sup>[25]</sup>. Other studies focused on the role of PPAR $\beta$ / $\delta$  in attenuating atherosclerosis progression, revealing that this isoform has an HDL-raising effect and anti-inflammatory activity within the vessel wall, where it participates in the down-regulation of chemokines production <sup>[26]</sup>.

Mechanisms of the anti-inflammatory effects of PPARy include the inhibition of the transcriptional activity of NF- $\kappa$ B, STAT-1, and AP-1 <sup>[27]</sup>. A direct relationship between TNF- $\alpha$  adipocyte secretion and a decrease in expression of PPARy has been reported <sup>[28]</sup>. Moreover, negative regulation of PPARy contributes to the antiadipogenic effects of TNF- $\alpha$ , whose increased production is relevant in obesity states <sup>[29]</sup>. In fact, several studies have also demonstrated a metabolic benefit related to the anti-inflammatory effects of targeting PPARy <sup>[30]</sup>.

All PPARs isoforms can have a role in regulating inflammatory responses, employing their interaction with various transcription factors stimulating inflammation, signal transducer, the formation of complexes between co-activators and co-repressors, and the modulation of different kinases <sup>[31]</sup>.

Thus, the need for more in-depth knowledge of PPARs activity derives from their key role in various metabolic processes, including lipid and glucose homeostasis and inflammatory disease, which makes them the ideal target for developing new pharmacological strategies.

PPAR agonists are currently used to treat many diseases, such as hyperlipidemia, insulin resistance, type 2 diabetes, cardiometabolic syndrome, and atherosclerosis. The latest generation of agonists is represented by the selective peroxisome proliferator-activated receptor modulators, indicated as SPPARMs. With respect to traditional ligands, they can act as dual partial agonists, binding to two isoforms of receptors. Moreover, they have the ability to produce particular conformational changes, which leads to the preferential activation of transcriptional factors <sup>[32]</sup>. Further progress is represented by pan agonists, whose beneficial effects result from the ability to bind and activate the diverse isoforms of PPARs, reinforcing the single activation mediated by selective agonists <sup>[33]</sup>.

#### The Importance of PPARy in IBDs

Maintaining a healthy gastrointestinal tract depends on external factors (diet, chemicals, drugs, stress) or endogenous factors (genetics, microbiota, efficient immune responses). The loss of equilibrium between these factors may determine the onset of diseases. However, the elements contributing to inflammation and bowel disease are not clear. It is not possible to define a single factor or gene responsible for these modifications. Considering the critical role of PPARs in inflammation, many studies have focused on the possible correlation between these receptors, IBD, and cancer. In particular, chronic intestinal inflammation represents the leading risk factor for the development of gastrointestinal malignancy. Patients with UC and CD have a significantly higher cancer susceptibility <sup>[34]</sup>.

The role of PPARs in inflammatory responses, which has already been described above, makes them possible actors in the pathogenesis of intestinal disorders and cancer. Particular attention has been given to PPARy since it is abundantly expressed in epithelial cells in the large and small intestines <sup>[Z]</sup>. Although the first evidence on the potential link between PPARy and intestinal disease established a correlation between this receptor expression and an increase in colon tumorigenesis, recently, many researchers have re-examined the association between PPARy and the risk of colorectal cancer (CRC) <sup>[35][36][37][38]</sup>.

Genetic studies have demonstrated that heterozygous intestinal-specific PPARy knockout enhanced tumor growth, evidencing PPARy as a tumor resistance factor <sup>[39]</sup>.

Interestingly, the activation of PPARy by mesalazine could be responsible for CRC prevention observed with this drug in IBDs <sup>[40]</sup>. In immune-deficient mice engrafted with human CRC cells, mesalazine administration reduces xenografts' growth via a PPAR-y-dependent mechanism <sup>[41]</sup>. Activation of PPARy by mesalazine is accompanied by induction of the tumor suppressor gene PTEN, activation of caspase-8 and caspase-3, and diminished expression of surviving and X-linked inhibitor apoptosis protein <sup>[42]</sup>.

However, the role of PPARy is not only related to tumorigenesis, because a lot of evidence suggests its involvement in inflammation diseases. For example, a down-regulation has been reported in PPARy expression in UC <sup>[37]</sup>, and a negative correlation has also been hypothesized with UC progression, because of the low level of PPARy mRNA in the mucosa of active UC patients compared with UC patients in remission <sup>[8]</sup>. Sugawara et al. demonstrated positive evidence for the association of allelic variation of the PPARy gene and CD <sup>[43]</sup>. These findings suggest that chronic inflammation could be caused by decreased levels in PPARy expression in the colon.

Among the distinctive features of IBDs' pathogenesis, there is real deregulation in cytokine production in inflamed colon areas. Studies on human biopsies and in vitro models have demonstrated that a broad set of molecules dominates the mucosal response, where the contribution of epithelial cells is predominant <sup>[44]</sup>. These soluble mediators include proinflammatory cytokines, such as TNF- $\alpha$ , IFN- $\gamma$ , IL-6, IL-12, IL-21, IL-23, IL-17, and anti-inflammatory cytokines, such as IL-10, TGF $\beta$ , IL-35 <sup>[4]</sup> and chemokines CXCL1, CXCL2, CXCL3, CCL20 <sup>[44]</sup>. In particular, the elevated production of IL-12, IL-23, IFN- $\gamma$ , and IL-17 seems to be characteristic of CD, while UC is usually associated with increased production of IL-3, IL-5, and IL-9 <sup>[5]</sup>.

PPARy distinguishes itself for the protective effects, including the modulation of cytokine/chemokine production and the negative regulation of macrophage activation <sup>[45]</sup>. In this scenario, it is not difficult to understand why studies have abundantly focused on the  $\gamma$ -isoform of PPARs and the possible mechanism through which this receptor could be involved in bowel inflammation (Figure 1).

The activation of PPARy determines a decrease in the production of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6, and the inhibition of transcription factors, including NF- $\kappa$ B, AP-1, STAT-1, and Intercellular Adhesion Molecule (ICAM-1), and matrix metallopeptidase 9 (MMP-9) <sup>[46]</sup>.

Several studies have shown that PPARy synthetic agonists can ameliorate gut inflammatory phenomena. Bassaganya-Riera et al.  $\frac{[47]}{1}$ , using in vivo models of IBD, provided molecular evidence that conjugated linoleic acid reduces colitis inflammation employing a PPAR  $\gamma$ -dependent mechanism. More recently, it was shown that the synthesized jasmonate analog J11-Cl (2-hydroxyethyl 5-chloro-4,5didehydrojasmonate), structurally similar to cyclopentenone prostaglandin 15d-PGJ<sub>2</sub>, increases PPARγ activity and exerts anti-inflammatory effects, determining a less severe form of intestinal inflammation in dextran sodium sulfate (DSS)induced colitis in mice. The treatment reduced pro-inflammatory cytokines and chemokines and increased antiinflammatory cytokines and growth factors <sup>[48]</sup>. Another research study also supports the role of PPARγ in the amelioration of inflammatory bowel disease. In trinitrobenzene sulfonic acid (TNBS)-induced colitis mice, the andrographolide-lipoic acid conjugate (AL-1) administration alleviates inflammation through inhibiting the expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 and down-regulating the expression of p65 and p-IkB, key regulators of NF- $\kappa$ B pathway. Moreover, COX-2 levels, which are regulated by NF- $\kappa$ B, were reported to control levels, and the expression of PPARγ was increased in AL-1 treated groups <sup>[49]</sup>. The modulation of PPARγ/NF- $\kappa$ B cascade in intestinal inflammation is related to p21-activated kinase 1 (PAK1), the results of which overexpressed and activated in IBDs <sup>[50]</sup>. In particular, TNF- $\alpha$  is responsible for the translocation and co-localization of p-PAK1 and p-65 in the nucleus. These events determine the transcriptional activation of NF- $\kappa$ B. Activated PAK1 blocks PPARy, increasing accumulation of p-65.

TNF-α stimulation can also induce the expression of COX-2, whose transcription can be regulated by several factors such as NF-κB and PPARs <sup>[51]</sup>. It has been demonstrated that this pro-inflammatory enzyme is induced in the human inflamed large intestine and IL-10 deficient mouse model of IBD <sup>[52][53]</sup>. COX-2 metabolizes free arachidonic acid (AA) into prostanoids, such as prostaglandins (PGs) and thromboxanes (TXs). The by-products cyclopentenone prostanoids, including 15-deoxy-12,13-didehydro-14,15-didehydro-PGJ<sub>2</sub> (15d- $\Delta^{12,14}$ -PGJ<sub>2</sub>), 12,13-didehydro-PGJ<sub>2</sub> ( $\Delta^{12}$ -PGJ<sub>2</sub>), and PGA<sub>2</sub>, are ligands of PPARy, suggesting an interaction between this receptor and COX-2 during inflammation <sup>[54][55]</sup>. Prostaglandins exert anti-inflammatory effects by inhibiting NF-κB mediated by the blockage of IkappaB kinase and activation of PPARy <sup>[56]</sup>.

Other evidence suggested the role of the cannabinoid system in IBD, since cannabinoid receptors 1 and 2 (CB1 and CB2) are increased in IBD colonic tissue [57]. Moreover, a strong increase of endocannabinoids (especially anandamide) was found in biopsies from patients with untreated UC [58]. The results of several studies support the hypothesis of a cross-talk between PPARy and the cannabinoid system in reducing inflammation. Liu et al. indicated PPARy as a molecular target for synthetic cannabinoids, demonstrating its possible use in various treatments [59]. Furthermore, the sesquiterpene  $\beta$ -caryophyllene (BCP) can reduce DSS-induced colitis in mice with a mechanism associated with CB2 and PPARy, which leads to the inhibition of pro-inflammatory cytokines and NF- $\kappa$ B [57].



**Figure 1.** Peroxisome proliferator-activated receptors-γ (PPARy) in IBDs. PPARγ belongs to the family of nuclear receptors. Its activation involves the translocation in nucleus and the heterodimerization with retinoid X receptor (RXR). The heterodimers bind to sequence-specific PPAR response elements (PPREs), stimulating the transcription of target genes. Corepressors maintain the target genes inactivated in absence of PPARγ ligands. The protective effects of PPARγ include the modulation of pro-inflammatory cytokines production, such as TNFγ, IL-6, the inhibition of transcription factors, including NF-kB, STAT-1, AP-1, and intercellular adhesion molecule and MMP-9. PPARγ also determines the downregulation of p65 expression and IkappaB kinase. In contrast, TNF-α activates NF-kB, which stimulates COX-2 to convert arachidonic acid in prostaglandins. The anti-inflammatory properties of prostaglandins are related to their ability to bind PPARγ, blocking NF-kB downstream events. PPARγ synthetic agonists can ameliorate IBD inflammation.

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