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GPR120/FFAR4: a potential new therapeutic target for inflammatory bowel disease

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Abstract:	Inflammatory bowel disease (IBD) whose major forms are Crohn's disease and ulcerative colitis, is characterized by chronic inflammation of the gut due to the loss of tolerance toward antigens normally contained in the gut lumen. G-protein-coupled receptor (GPR) 120 has gained considerable attention as a potential therapeutic target for metabolic disorders due to its implication in the production of the incretin hormone glucagon-like peptide 1 and the secretion of cholecystokinin. Recent studies have also highlighted the role of GPR120 in regulating immune system activity and inflammation. GPR120, expressed by intestinal epithelial cells, pro-inflammatory macrophages, enteroendocrine L cells, and CD4+T cells, suppresses pro-inflammatory and enhances anti-inflammatory cytokine production, suggesting that GPR120 might have a pivotal role in intestinal inflammation and represent a possible therapeutic target in IBD. This narrative review aims at summarizing the role of GPR120 in the maintenance of intestinal homeostasis through the analysis of the most recent studies.

GPR120/FFAR4: a potential new therapeutic target for inflammatory bowel disease

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Key Messages

This narrative review describes preclinical evidence sustaining the role of GPR120/FFAR4 fatty acid receptor in the control of intestinal inflammation in inflammatory bowel disease (IBD). GPR120, expressed by intestinal epithelial cells, macrophages, enteroendocrine L cells, and $CD4^+$T cells suppresses pro-inflammatory and enhances anti-inflammatory cytokine production, suggesting that GPR120 could represent a possible therapeutic target in IBD.

Abstract

Inflammatory bowel disease (IBD) whose major forms are Crohn's disease and ulcerative colitis, is characterized by chronic inflammation of the gut due to the loss of tolerance toward antigens normally contained in the gut lumen. G-protein-coupled receptor (GPR) 120 has gained considerable attention as a potential therapeutic target for metabolic disorders due to its implication in the production of the incretin hormone glucagon-like peptide 1 and the secretion of cholecystokinin. Recent studies have also highlighted the role of GPR120 in regulating immune system activity and inflammation. GPR120, expressed by intestinal epithelial cells, pro-inflammatory macrophages, enteroendocrine L cells, and $CD4^{+}$T cells, suppresses pro-inflammatory and enhances anti-inflammatory cytokine production, suggesting that GPR120 might have a pivotal role in intestinal inflammation and represent a possible therapeutic target in IBD. This narrative review aims at summarizing the role of GPR120 in the maintenance of intestinal homeostasis through the analysis of the most recent studies.

1. Introduction

Inflammatory bowel disease (IBD), whose major forms are Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation of the gastrointestinal tract[1]. IBD heavily impacts the quality of patient's life causing persistent symptoms like abdominal pain, diarrhea, weight loss, fatigue, rectal bleeding, nausea, and fever, whose severity depends on the grade of the underlying inflammatory activity[2]. In addition, chronic inflammation determines progressive and irreversible organ damage thus leading patients to surgery and life-threatening complications[3].

Although the pathogenesis of IBD has been intensively investigated in the last decades, its etiology remains unclear. Multiple factors are believed to concur to the development of IBD, such as genetic, immune, and environmental factors[4]. Data from genome-wide association studies (GWAS) identified several gene allele variants associated with the increased risk to develop IBD[5]. These genes are involved in several crucial pathways involved in intestinal homeostasis, including barrier function, epithelial restitution, microbial defense, innate and adaptive immune regulation, and metabolic pathways[6]. In physiological conditions, different immune cell types are present along the gastrointestinal tract, including dendritic cells (DCs), macrophages, natural killer (NK) cells, natural killer T (NKT) cells, and innate lymphoid cells (ILCs), but an altered function of these cells has been observed in IBD patients, contributing to the breakdown of immunological tolerance toward antigens contained in the gut lumen[7].

In spite of a clear genetic predisposition, IBD also depends on exposure to environmental factors. Among them, early use of antibiotics, smoking habit, and the diffusion of westernized diet in developed countries are associated with a steep increase in IBD incidence[8].

Long-chain fatty acids (LCFAs) contain 13–21 carbons and can be classified into different types based on the presence of double bonds, such as saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). Unsaturated fatty acids can be further classified into different types based on the location of the first double bond from the methyl end of the carbon chain, resulting in the categories

of ω-3, ω-6, and ω-9 fatty acids [9]. The specific health benefits and effects of each type of LCFA are influenced by their unique structures and biochemical properties. ω-3 fatty acids, in particular, have received considerable attention for their potential protective effects on cardiovascular health, cognitive function, and reducing inflammation. ω-6 and ω-9 fatty acids also contribute to various physiological processes but a balanced intake in relation to ω-3 fatty acids to support optimal health has been proposed [10]. Several studies have suggested that increasing the intake of LCFAs may reduce the risk of IBD relapse, progression, and severe course [11–13]. However, it is important to note that a recent meta-analysis pointed out the need for more rigorous studies due to the limited quality of evidence available [14].

There are several mechanisms through which fatty acids can impact inflammatory cell function and inflammatory processes, such as incorporation into the phospholipids of inflammatory cell membranes, acting as precursors of extracellular signaling molecules (e.g. prostaglandins, PG) directly acting on Free Fatty Acid Receptors (FFARs) [15]. FFARs are trans-membrane receptors belonging to the family of rhodopsin-like G protein-coupled receptors (GPCRs) categorized according to ligand length profile, indeed, LCFAs activate FFAR1 and FFAR4.

FFAR4, also called GPR120, has been proven to reduce atherosclerosis risk, improve insulin sensitivity and ameliorate IBD-related symptoms[16]. In large part, the interest in this receptor as a potential therapeutic target has been driven by the reported capacity to promote the secretion of incretins, including GLP-1, which has been shown to increase insulin, decrease glucagon levels, and food intake leading to major benefits on blood glucose control and weight loss [17]. The importance of GPR120 has been supported by studies utilizing selective GPR120 agonists and knockout mouse models in fact, studies on GPR120 knockout mice (KO) have demonstrated increased adiposity, insulin resistance, and glucose intolerance compared to wild-type mice. [18,19].

Recently, it has been shown that GPR120 expression is not limited to intestinal epithelial cells but, it is also present in several immune cell types, including macrophages and $CD4^{+}$T cell[18,20,21]. In these

cells GPR120 activation suppresses pro-inflammatory and enhances anti-inflammatory cytokine production reducing disease severity in murine models of colitis[18,20]. These results suggest that GPR120 could play a key role in IBD.

The purpose of this review is to outline the structure of GPR120 agonists and to describe the role of GPR120-mediated signaling in the maintenance of intestinal immune homeostasis through the analysis of *in vitro* and *in vivo* models. Different databases were searched for this purpose, including MEDLINE (PubMed), Google Scholar, ScienceDirect, Scopus, Cochrane, SID, and SciFinder.

2. GPR120 signalling.

GPR120 belongs to the rhodopsin receptors family and shares a very low sequence homology with another FFAR, GPR40 or FFAR1. GPR120 has been reported to be present in two isoforms: a long isoform (377 residues, GPR120L) and a short isoform (361 residues, GPR120S)[22]. The main difference is a 16-residue segment in the third intracellular loop of the long isoform responsible for different signaling pathways[22]. The two isoforms have identical endogenous substrate binding sites known as orthosteric binding pockets and share the same endogenous substrates that upon binding, activate the downstream signaling through second messengers. Therefore, in humans, the functional significance of the two isoforms remains unclear[23].

Researchers have relied on homology modeling, a computational technique to build reliable 3D structural models of GPR120 (Figure 1). These models have helped predict the binding site of GPR120 and revealed the importance of specific residues for ligand binding.

Unsaturated fatty acids, including ω-3, ω-6, and ω-9 FAs, serve as ligands for GPR120. Among them, docosahexaenoic acid (DHA) and α-linolenic acid (ALA) are the most potent and commonly observed GPR120 agonists [24]. However, recent studies have shown that both ω-3 and ω-6 PUFAs exhibit similar anti-inflammatory effects upon binding to GPR120, although with different kinetics [25]. It is important to note that the selectivity of ω-3 and ω-6 PUFAs is limited due to their interaction with GPR40 as well [26]. Therefore, the identification of GPR120-selective agonists is still missing.

Several studies have focused on developing selective agonist ligands for GPR120. The structures of GPR120 agonists are shown in Figure 2. Most of the reported ligands are carboxylic acids that are assumed to mimic endogenous LCFA agonists[27]. Researchers have attempted to develop agonist ligands that are selective for GPR120, starting from the first characterized synthetic agonist ligand GW9508 which was initially reported to be active also against FFA1. In order to develop a selective GPR120 agonist, NCG21 ligand, which showed an activity10-fold higher against GPR120 as compared to FFA1[28], was synthesized. Commercially available GSK137647A (N-Mesityl-4-methoxybenzenesulfonamide) ligand, behaves as a selective agonist of GPR120 and has been reported to have a 50-fold selectivity over FFA1[29]. Shimpukade et al.[30] synthesized TUG-891, the first potent, and selective GPR120 agonist, optimized from a series of FFA1 agonists originally derived from fatty acids that showed nearly 1000-fold selectivity for FFA4 over FFA1. The role of the amino acid arginine (Arg) at position 99 in driving the function of TUG-891 against FFA4 protein has been highlighted in several studies[22,30]. TUG-1197 was synthesized from a series of cyclic sulfonamide GPR120 agonists[31] and displayed no detectable activity against FFA1 as compared to GPR120 receptor. Additionally, Oh et al.[32] designed CpdA (3-[2-chloro-5-(trifluoromethoxy) phenyl]-3-azaspiro [5.5] undecane-9-acetic acid) molecule and examined its selectivity for GPR120 receptor (logEC50 (M) = -7.62 ± 0.11) compared to the insignificant activity towards FFA1. Finally, DFL23916, showed very high selectivity towards human GPR120 (for both long and short isoforms) [33].

Recently, using cryomicroscopy electron microscopy and structural analysis, six structures of GPR120 in complex with different unsaturated fatty acids and a synthetic agonist were obtained. It was discovered that unsaturated fatty acids containing ω-3 double bonds adopt an "L" shape within the receptor which are specifically recognized by aromatic residues present in the GPR120 ligand pocket. Notably, upon binding to GPR120, ω-3 fatty acids demonstrate selective activation of Gs proteins, indicating their potential for modulating GPR120-mediated signaling pathways. These findings provide a rationale for the development of selective GPR120 agonists [34].

The activation of GPR120 triggers a range of downstream signaling pathways involving G proteins coupled receptors (Gαs, Gαi, Gαq) and β-arrestins [35]. These pathways contribute to diverse cellular responses, including metabolic regulation, anti-inflammatory effects, and modulation of intracellular calcium levels[36].

Upon activation, GPR120 can couple with Gαs proteins, leading to the activation of adenylyl cyclase and a subsequent increase in cAMP levels. This activation triggers downstream events mediated by protein kinase A (PKA), influencing various cellular processes, including adipogenesis [36].

In addition, GPR120 can couple with Gαi proteins, resulting in the inhibition of adenylyl cyclase and a decrease in cAMP levels. This modulation affects cellular responses such as reducing inflammation and inducing metabolic alterations. Notably, the Gi function of GPR120 plays a crucial role in promoting insulin secretion in pancreatic islets and inhibiting ghrelin secretion in gastric cells [37,38].

Activation of GPR120 can also promote the coupling with Gαq proteins. This interaction activates phospholipase C (PLC), leading to the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces the release of calcium ions (Ca2+) from intracellular stores, while DAG activates protein kinase C (PKC). This pathway is involved in GPR120-mediated glucose transporter member 4 (GLUT4) translocation in adipose tissues [18] and GLP-1 secretion both in vitro in STC-1 cells and in vivo following oral administration [39,40].

Furthermore, GPR120 activation recruits β-arrestins 2, which play a role in receptor desensitization, internalization, and downstream signaling. β-arrestins can activate mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK) and p38 MAPK. They are involved in regulating cell proliferation, differentiation, and inflammatory responses [36,41].

It should be noted that the specific signaling pathways activated by GPR120 may vary depending on the ligand, cell type, and activation context. These multifaceted pathways enable GPR120 to elicit a wide range of cellular responses.

3. Role of GPR120 in regulating intestinal and immune homeostasis

3.1. GPR120 on Intestinal Epithelial Cells

GPR120 is expressed in epithelial cells and appears to be involved in the maintenance of mucosal barrier integrity and in the regulation of the inflammatory response[21]. To explore the functional role of GPR120 in the epithelial compartment, several studies have been performed as summarized in Table 1.

In Caco-2 cells, an immortalized cell line of human colorectal adenocarcinoma used as *in vitro* model of intestinal barrier[42], GPR120 stimulation by ω-3 fatty acids and synthetic agonists GW9508 and TUG-891 reduced the expression pro-inflammatory cytokines preventing the activation of NF-κB and c-Jun NH 2 -terminal kinase (JNK) by β-arrestin2. Briefly, after binding its agonists, GPR120, forms a complex with β-arrestin2 and the TAK1-binding protein (TAB1). This process prevents the association between TAB1 and TAK1 consequently reducing TAK1 activation[43,44]. TAK1/TAB1 is a convergence point of several signaling pathways including those generated by toll-like receptor 4 (TLR4) and TNF receptor (TNFR) where it is implicated in the activation of IκB kinase (IKK) and NF-κB nuclear traslocation [43], JNK activation and AP-1-dependent gene expression[45]. Therefore, the mitigation of TAK-1 activation by GPR120 leads to the reduced expression of proinflammatory genes[46].

In addition to NF-κB inhibition, GPR120 activated by ω-3 and ω-6 fatty acids, although with different kinetics, triggers in Caco-2 as well as in HCT116 and HT-29 colorectal cell lines, two independent intracellular signaling events involved in intestinal homeostasis: the cytosolic accumulation of Ca^{2+} due to Gαq engagement and the activation of extracellular signal-regulated kinases (ERK)1/2, a

mitogen-activated protein (MAP) kinase, through Raf-1-dependent transactivation of epidermal growth factor receptor (EGFR) [47,48].

Both cytosolic Ca^{2+} increase and pERK1/2 activation are involved in GPR120-induced secretion of GLP-1 and CCK by enteroendocrine cells[49]. In intestinal secretin tumor cell line (STC-1), used as a model of intestinal enteroendocrine cells, CCK secretion is promoted by ω-3 fatty acids upon ingestion of fat by increasing intracellular Ca^{2+} concentration and protein kinase A-dependent L-type Ca^{2+}channel depolarization[50].

The enteroendocrine system might have a role in the pathogenesis of IBD[51] as suggested by the alteration of absolute enteroendocrine cells number and their related hormones in both IBD patients and murine models of colitis. Indeed, GLP-1 may reduce systemic inflammation directly improving intestinal epithelial barrier function, promoting the differentiation and activation of regulatory T cells (Treg) and modulating the activity of intraepithelial lymphocytes (IELs), macrophages and dendritic cells. In addition, GLP-1 can also reduce inflammation indirectly by improving glucose metabolism and preventing the accumulation of proinflammatory fat tissue[52]. CCK is a potent neuropeptide released during the feeding process and may also take part in the modulation of the mucosal immune system, attenuating leukocyte migration, inhibiting DCs activation, and regulating both T and B lymphocytes[51].

GPR120 also appears to be involved in mucus barrier formation[53]. Indeed, in mice with a conditional deletion of GPR120 in intestinal epithelial cells, the expression of mucin 2 (MUC2), a component of the mucus barrier that prevents the direct contact between intestinal bacteria and colonic epithelial cells, resulted significantly reduced as compared to wild-type (WT) mice[53].

Interestingly, the transcription of GPR120 and GPL1 in intestinal epithelial cells were found to be modulated by the presence of bacteria belonging to the Firmicutes, Bacteroides, and Proteobacteria phyla, the misbalance of which is documented in IBD patients[54].

These results support the involvement of GPR120 in the maintenance of intestinal barrier, though, the mechanisms by which GPR120 exerts this function and its role in inducing chronic inflammation need further investigation.

3.2. GPR120 on Immune Cells

IBD is characterized by a prominent infiltration in the gut lamina propria of inflammatory cells, such as T and B lymphocytes, macrophages, neutrophils, mast cells and plasma cells [55]. The potential involvement of GPR120 in IBD is further suggested by its expression in cells of the innate and adaptive immune systems such as macrophages, DCs, and T cells[18,20].

In RAW 264.7 cells, a monocyte/macrophage-like cell line, the GPR120 agonists DHA and GW9508 significantly suppressed the induction of proinflammatory mediators by the TLR4 ligand lipopolysaccharide (LPS), a structural component of the outer membrane of gram-negative bacteria, and by TNFR ligand TNF-α [18] (Figure 3A). In the context of IBD, the defective or leaky thigh junction intestinal barrier allows paracellular penetration of LPS and other luminal antigens [56]. TLR4 activation by LPS initiates different intracellular signaling pathways, including MyD88- and TRIF-dependent signaling pathwaies[57]. GPR120 agonist's anti-inflammatory activity occurred by inhibiting MyD88-dependent pathway leading to repression of NF-kB and AP-1 through the mechanism previously discussed which involves β -arrestin-2 internalization and its association with TAB1[18].

In vitro studies demonstrated that CpdA blocked chemotaxis of macrophages induced by adipocyte conditioned medium, and this effect was lost in GPR120 deficient macrophages[32]. Accordingly, *in vivo* treatment with CpdA of mice fed with high-fat diet (HFD), substantially decreased pro-inflammatory M1-like macrophages while increasing anti-inflammatory M2-like macrophages and Tregs in the adipose tissue. Moreover, the expression of the pro-inflammatory genes *Tnf-α, Il-6, Ccl2* and *Il-1β,* were markedly reduced while anti-inflammatory *Il-10, Clec7a, Clec10a* and *Chil3* were increased in mice treated with CpdA [32].

GPR120 is highly expressed in $CD4^+$ T cells which play a major role in the pathogenesis of IBD[58]. Indeed, CD is driven by Th1 and Th17 cells while in UC a Th2-mediated immune response prevails[59]. Activation of GPR120 with CpdA inhibited Dextran Sulphate Sodium (DSS)-induced colitis in mice by upregulating IL-10 expression in CD4+ Th1 cells. Conversely, mice with GPR120-deficient CD4+ T cells developed more severe colitis after treatment with DSS. Mice with GPR120-deficient CD4+ T cells also showed increased production of pro-inflammatory cytokines, TNF-α, IL6, and IL-17A, and decreased levels of IL-10[20].

The mammalian target of rapamycin (mTOR) is involved in several anabolic and catabolic processes in response to nutrients[60]. GPR120 activation promoted IL-10 production in CD4+ T Th1 cells with two different mechanisms both involving mTOR activation[20]. CpdA-mediated activation of GPR120 was shown to induce Stat3 phosphorylation and Blimp1 activation in an mTOR-dependent manner. At the same time, GRP120-induced mTOR activation promoted glycolysis indirectly regulating hypoxia-inducible factors 1 (HIF1)-mediated signaling[20].

The inhibition of M1 macrophage chemotaxis and the increase of IL-10 in CD4 + T cells, make GPR120 a potential target in the treatment of chronic inflammatory diseases (Figure 3B).

3.3. Role of GPR120 in different murine colitis models

GPR120 is widely expressed in the mammalian intestinal tract, particularly in the colon[61], and its expression is modulated by fat intake and inflammation[20,62]. Mice fed with a diet rich in fish oil and flaxseed oil significantly increased the expression of GPR120 and decreased TNF-α in the gut[63].

In the DSS model of colitis, where administration of DSS results in the induction of a very reproducible acute inflammation limited to the colon[64], branched palmitic acid esters of hydroxy stearic acids (PAHSAs) markedly reduced gut inflammation by recruiting GPR120 and reducing pro-inflammatory cytokines production. In this model PAHSA treatment also reduced Th1 polarization and consequently IFN-γ expression[65].

Moreover, oral feeding of CpdA inhibited DSS colitis development in mice, as demonstrated by reduced weight loss, colon length preservation and lower pathology scores. CpdA also decreased the expression of pro-inflammatory cytokines and increased IL-10 in DSS-treated mice[20]. On the contrary, DSS-treated CD4+ cells-conditional GPR120 KO mice showed more severe disease, characterized by high expression of TNFα, IL-6, and decreased IL-10[20]. Similar results were obtained in CD4+ GPR120 KO mice infected with *Citrobacter rodentium,* an enteric bacterial strain which causes a form of enteritis similar to that induced by human IBD-related enteropathogenic *Escherichia coli*[20].

In the murine High Fatty Diet (HFD) model of metabolic syndrome and chronic inflammation[66], ω-3 decreased pro-inflammatory cytokine expression in adipose tissue and this effect was dependent on GPR120 expression. In particular, administration of ω-3 fatty acids promoted the accumulation of anti-inflammatory M2 macrophages in the in adipose tissue while decreasing the accumulation of M1 cells[18]. This result was confirmed by Oh and colleagues who demonstrated that GPR120 stimulation by ω-3 fatty acids and CpdA decreased adipose tissue macrophage infiltration and reduced inflammatory gene expression[32]. Moreover, GPR120 activation with Perilla Oil, a rich source of ω-3 fatty acids, was found to reduce TAK1 and NF-κB activation[67]. Lines of evidence indicate a functional interplay between intestinal permeability and inflammation, and the accumulation of visceral fat[68]. Accordingly, HFD and obesity have been shown to worsen colitis in a mouse model of colitis[69]. Therefore, GPR120-mediated signaling in the fat tissue could indirectly contribute to the control of intestinal inflammation.

It is widely known that genetic polymorphisms at the IL-10 locus confer an increased risk to develop IBD[70]. Accordingly, mice with targeted deletion of IL-10 develop spontaneous inflammation of the colon as demonstrated by a dense inflammatory infiltrate characterized by lymphocytes, macrophages, and neutrophils[70]. DHA administration improved experimental chronic colitis and prevented body weight loss in IL-10-deficient mice. This effect was associated with reduced

expression of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-17A. TAK1/IKK-α/IkB-α/p65 pathway has been demonstrated up-regulated in IL-10 KO mice compared to the WT. Conversely, a marked decrease in the expressions of these proteins was observed in the colon of DHA-treated mice[71].

In the azoxymethane (AOM)/DSS model of colitis-associated colorectal cancer, selective loss of GPR120 in intestinal epithelial cells impaired epithelial barrier function, induced bacterial translocation and dysbiosis leading to high epithelial cell proliferation and tumor development[53]. Wnt/β-catenin signaling pathway, known to be involved in cell growth, differentiation, and apoptosis[72], was found altered in absence of GPR120[53].

In contrast to studies supporting the anti-inflammatory effect of GPR120-mediated signal in T cells, it was recently shown that overexpression of GPR120 in epithelial cells worsened colitis in mice. This effect was dependent on GPR120 expressed by epithelial cells and IL-33-mediated block of Treg suppressive function[73].

Overall, data originated from multiple models, summarized in Table 2, confer to GPR120 a relevant role in the suppression of inflammation in the gut and adipose tissue, two closely interacting tissues in IBD[74]. Though, the specific contribution of GPR120 signaling in different intestinal cell compartments in patients affected by IBD needs to be further defined.

3.4.GPR120 in IBD patients

Many clinical trials have examined the effect of dietary fat on IBD development with contrasting results[16]. Recently, Mozaffari et al.[75] published a meta-analysis of observational studies, whose aim was to investigate the association between fish consumption and ω-3 fatty acids intake with the risk of IBD. An inverse association between fish consumption and the incidence of IBD was found in this study.

GPR120 could contribute, at least partially, to the positive effect of a diet rich in ω-3 fatty acids. GPR120 expression is increased and positively correlated with IL-10 production in biopsies of patients affected by UC as compared to healthy controls[20]. The increase of GPR120 expression in IBD patients suggests its pathogenetic role but the use of GPR120 agonists for therapeutic purposes has not been explored so far.

4. Conclusion

Several *in vivo* and *in vivo* data highlight the role of GPR120 in intestinal homeostasis. In intestinal epithelial cells, GPR120 stimulation by ω-3 fatty acids and synthetic agonists inhibits NF-κB transcription and induces GLP-1 and CCK secretion. NF-κB plays a key role in the initiation and perpetuation of the inflammatory process. GLP1 and CCK, in addition to their essential role in the digestive process, play an important role in reducing systemic inflammation by modulating the differentiation and activation of several immune cell types including Treg, T helper cells, macrophages and DCs. In CD4+ T cells, GPR120 engagement inhibits pro-inflammatory cytokines production (such as TNF-α, IFN-γ, and IL-17A) and increases IL-10 concentration. In different murine models of colitis, treatment with ω-3 fatty acids and GPR120 synthetic agonists reduces inflammation and disease severity, and this effect has been associated with the inhibition of pro-inflammatory cytokine expression and increased IL-10.

Taken together these results provide clear evidence that GPR120 plays a central role in the maintenance of intestinal immune homeostasis, and it might represent a potential therapeutic target in IBD. In particular, it would be interesting to understand whether expression of GPR120 relates to the grade of inflammation and disease stage, and whether selective GPR120 agonists have an anti-inflammatory effect in IBD patients with high receptor expression.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

A.D.P. and A.K. wrote the article and created tables and figures. S.O. and A.F. reviewed the article. M.C.F. critically reviewed the article and supervised the project. All authors contributed and approved the final version of the manuscript.

Data Availability Statement

The data underlying this article are available in the article.

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Tables

Table 1. GPR120 signaling pathway in intestinal epithelial cells.

Cellular line	Signaling pathway	References
Caco-2	GPR120 activation induces different signaling pathways: it increases the cytosolic accumulation of Ca^{2+} due to Gαq activation, induces ERK1/2 expression through epidermal growth factor receptor transactivation involving Raf-1 kinase, and inhibits NF-κB transcription factor through the activation of β-arrestin2/TAB1 signaling that blocks TAK1/TAB1 association, reducing the expression of pro-inflammatory cytokines.	[48]
HCT116	GPR120 activation increases the cytosolic accumulation of Ca^{2+} due to Gαq activation, inducing the secretion of GLP-1 and CCK.	[47]

HT-29	GPR120 activation induces different signaling pathways: increasing the cytosolic accumulation of Ca^{2+} due to Gαq activation.	[47]
STC-1	GPR120 activation increases the cytosolic accumulation of Ca^{2+} through depolarization of L-type Ca2+channel by protein kinase A, inducing the secretion of GLP-1 and CCK.	[50]

Abbreviation: GLP-1: glucagon-like peptide 1; CCK: cholecystokinin; TAK1: kinase activated by the growth factor beta; TAB1: TAK1-binding protein; ERK1/2: extracellular signal-regulated kinases 1/2.

Table 2. GPR120 agonist effect of different murine colitis models

Murine model	**GPR120 agonist effect**	**References**
DSS	CpdA inhibits colitis progression with decreased weight loss, increased colon length, lower pathology scores, and lower proinflammatory cytokine production, as well as increased IL-10 production. PAHSAs markedly reduces gut inflammation by reducing IFN-γ from $CD4^{+}$T cells acting on the capacity of DCs to induce Th1 polarization. Selective loss of GPR120 in epithelial cells ameliorates colitis upregulating ZBED6 transcription levels, which leads to an increase IL33 expression and Treg recruitment.	[20,65,73]

Citrobacter rodentium infection	CpdA inhibits colitis progression with decreased weight loss, increased colon length, and lower pathology scores.	[20]
HFD	ω-3 fatty acids decrease pro-inflammatory M1 and increased anti-inflammatory M2 macrophages in adipose tissue. Moreover, Perilla Oil, a rich source of ω-3 fatty acids, reduces TAK1 activation by LPS or TNF-α which in turn inhibits the activation of NF-κB.	[18,32,67]
IL-10 KO	DHA administration improves experimental chronic colitis and body weight loss by reducing pro-inflammatory cytokines, probably acting through the downregulation of TAK1/IKK-α/IkB-α/p65 pathway.	[71]
AOM/DSS	Selective loss of GPR120 in intestinal epithelial cells caused a dysregulation of Wnt/β-catenin pathway leading to increased cell proliferation and tumor incidence.	[53]

Abbreviation: DSS: dextran sulfate sodium; PAHSAs: palmitic acid esters of hydroxy stearic acids; DCs: dendritic cells; ZBED6: Zinc Finger BED-Type Containing 6; TAK1: kinase activated by the growth factor beta; LPS: lipopolysaccharide; DHA: docosahexaenoic acid; AOM: Azoxymethane; Wnt: Wingless-related integration site.

Figure Legends

Figure 1. 3D homology model of human GPR120S docked with TUG-1197 ligand.

Figure 2. Chemical structures of agonist ligands of GPR120/FFA4

Figure 3. Possible mechanisms of action of GPR120 on immune cells. (**A**) In macrophages, after internalization, GPR120 competitively binds TAB1, via β-arrestin2 (βARR2), consequently attenuating an inflammatory response induced by TLR or TNF signaling. (**B**) In $CD4^{+}$T cells, a trigger of GPR120 induces mTOR activation that positively regulates Stat3-Blimp1 and HIF1 pathways, essential for IL-10 production.