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Review

Bioactive lipids in inflammatory bowel diseases – From pathophysiological alterations to therapeutic opportunities

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ABSTRACT

Inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis, are lifelong diseases that remain challenging to treat. IBDs are characterized by alterations in intestinal barrier function and dysregulation of the innate and adaptive immunity. An increasing number of lipids are found to be important regulators of inflammation and immunity as well as gut physiology. Therefore, the study of lipid mediators in IBDs is expected to improve our understanding of disease pathogenesis and lead to novel therapeutic opportunities. Here, through selected examples – such as fatty acids, specialized proresolving mediators, lysophospholipids, endocannabinoids, and oxysterols – we discuss how lipid signaling is involved in IBD physiopathology and how modulating lipid signaling pathways could affect IBDs.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two main manifestations of chronic relapsing remitting inflammatory conditions of the gastrointestinal tract known as inflammatory bowel diseases (IBDs). The pathogenesis of IBDs is complex and results from an interplay between genetic predisposition and environmental factors leading to a dysregulated immune response, notably against the microbiota. Abdominal pain, diarrhea and rectal bleeding accompanied by systemic symptoms such as fever, weight loss and fatigue characterize both CD and UC. However, although both diseases are cytokine-driven, CD is mainly associated with a Th1/Th17 immune response, while UC is associated with a Th2 immune response [1]. Classic treatment for IBDs includes anti-inflammatory and immunosuppressive medications such as 5-aminosalicylic acid derivatives, corticosteroids, and azathioprine and derivatives. While effective in controlling flares or maintaining remission, these treatments vary in their long-term effectiveness, their tolerability and toxicity. These agents block inflammatory events regardless of the initiating pathway or defect. Anti-TNFα antibodies ushered in a new era of biologic drugs targeting major effector inflammatory cytokines, thus adding to the therapeutic arsenal of IBDs [2]. However, some patients stop responding to anti-TNFα antibodies while others do not respond at all. Therefore, it is crucial to develop drugs or combinations of drugs with favorable side-effect profiles. In this context, newer anti-TNFα antibodies and agents targeting other inflammatory cytokines such as IL-12 or IL-23 [3,4] are under development, as well as anti-adhesion molecules aimed at decreasing leukocyte trafficking to the gut [3–5]. Inhibitors of the JAK-STAT pathway are also being studied, as they would simultaneously block several inflammatory pathways [3,4,6]. The development of modulators of the sphingosine-1-phosphate receptors reinforced the importance of lipid mediator signaling in IBD pathogenesis [5,7]. Indeed, as we illustrate in this review, lipid mediators are involved in many facets of the pathogenesis of IBDs and could provide targets to be studied, alone or in combination with other anti-

Abbreviations: 2-AG, 2-arachidonoylglycerol; 25-OHC, 25-hydroxycholesterol; 4β-OHC, 4β-hydroxycholesterol; 7α,25-diOHC, 7α,25-dihydroxycholesterol; AA, arachidonic acid; AEA, *N*-arachidonoylethanolamine; CD, Crohn's disease; CH25H, cholesterol-25-hydroxylase; COX, cyclooygenase; DHA, docosahexaenoic acid; DP, prostaglandin D receptor; DSS, dextran sulfate sodium; EP, prostaglandin E receptor; EPA, eicosapentaenoic acid; FFA, free fatty acid receptor; GPCR, G protein-coupled receptor; GPR183, G-protein coupled receptor 183 also known as Epstein-Barr virus-induced G-protein coupled receptor 2 (EBI2), receptor for 7α,25-diOHC; GWAS, genome-wide association study; IBD, inflammatory bowel diseases; LOX, lipoxygenase; LPA, lysophosphatidic acids; LPC, lysophosphatidylcholines; LPE, lysophosphatidylethanolamines; LT, leukotriene; LXA4, lipoxin A4; LXR, liver X receptors; NAE, *N*-acylethanolamine; OHC, oxysterol; PG, prostaglandin; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator-activated receptors; ROR, retinoic acid related (RAR)-related orphan receptors; SCFA, short-chain fatty acid; SPM, specialized pro-resolving mediators; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis.

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inflammatory drugs, for the management of IBDs.

2. IBD pathogenesis in a nutshell

The pathogenesis of IBDs is multifactorial and it is important to understand the various factors and pathways at play in order to develop new and effective treatments. The molecular mechanisms of IBD development and progression remain unclear; however, their etiology has been linked to genetic susceptibilities coupled with environmental factors. Among the environmental factors, the gut microbiota, rather than conventional pathogens, has been implicated as a driver of the dysregulated immunity in IBDs. Pathway paradigms highlighted by IBD genetics put forth the role of the intestinal barrier function and innate and adaptive immunity in disease pathogenesis [8]. Therefore, IBDs can be summarized as abnormal mucosal immune responses facilitated by microbial factors and epithelial cell abnormalities.

The normal gut consists of an epithelial barrier, the mucosal immune system, and a number of stromal/supportive cells, which all display immune function. A monolayer of polarized epithelial cells lines the luminal surface of the gastrointestinal tract and forms a physical and functional barrier separating the complex luminal milieu and the host [9]. This selective barrier constitutes the first line of defense against bacteria and other microorganisms and plays an important role in gut homeostasis. It is permeable to nutrients and essential macromolecules but constitutes an obstacle for luminal antigens, intestinal bacteria, and harmful macromolecules. These cells also possess pathogen-sensing mechanisms that play a role in innate immunity. Epithelial cells are joined together by a highly organized apical junctional complex that includes tight junctions – constituted by different proteins such as occludin, zonula occludens-1 (ZO-1) and claudins [10] – and adherens junctions that seal the intercellular space [11]. A pre-epithelial layer, formed of mucins secreted by goblet cells, IgA and antimicrobial peptides, enhances the intestinal barrier and constitutes an important component of the innate immune response of the intestinal mucosa. The continuous, hydrophobic and adherent mucus layer protects the intestinal epithelium from potentially pathogenic bacteria. Tight junctions can be disrupted by pathogens such as bacteria, viruses and parasites as well as by cytokines and inflammatory mediators resulting from host inflammatory reactions [12]. This leads to an increase in intestinal permeability, allowing noxious substances present in the lumen, including bacteria, bacterial toxins, and digestive food products to come in close contact with intestinal cells [11]. Therefore, a dysregulation of the intestinal barrier function has been associated with a number of diseases, both intestinal such as IBDs and systemic [10].

The mucosal innate immune system is a key regulator of the functional integrity of the mucosa. The role of this immune system is to detect bacteria and antigens at the mucosal surface, differentiate between commensal microbiota and pathogens, and react accordingly. Indeed, a state of immune tolerance exists in the gut where the immune system does not react to commensal microbiota. Specialized epithelial cells, such as Paneth cells that secrete anti-microbial peptides, goblet cells that secrete several peptides including mucin-2, and M cells that transport by pinocytosis macromolecules, IgA complexes and microbes to antigen-presenting cells, contribute to innate immunity and have been implicated in IBD pathogenesis.

Immune cells residing within the gastrointestinal tract constitute the gut-associated lymphoid tissue that is composed of lymphocytes distributed in the mucosa, organized lymphoid structures such as Peyer's patches as well as dendritic cells and macrophages. Intestinal lymphoid tissues have an essential function in maintaining homeostasis. In mice, increased lymphoid tissue formation was correlated with the severity of intestinal inflammation [13,14]. Hyperplastic lymphoid aggregates are found in IBDs and were suggested to contribute to IBD pathology in humans [15]. Innate lymphoid cells, although lacking classical antigen receptors, sense environmental cues via intracellular receptors that act as transcription factors or via cell surface G protein-coupled receptors (GPCR) that can regulate immune cell migration. One such GPCR is the lipid receptor GPR183 (or EBI2, Epstein-Barr Virus-Induced GPCR 2) [13].

Resident dendritic cells are the main antigen-presenting cells present in the lamina propria. Their role is to monitor continuously the luminal environment. In response to activation, by for instance TLR ligands, these dendritic cells produce IL-23, which is one of the main drivers of intestinal inflammation in murine models of IBDs [16]. In a normal state, resident intestinal macrophages show a state of hyporesponsiveness in response to microbial ligands or cytokines/chemokines. However, following inflammatory stimuli, circulating monocytes migrate to the intestinal mucosa where they undergo differentiation into macrophages and participate to the inflammatory reactions. Activated macrophages that produce TNF-α and IL-23 are implicated in the development of colitis [4,17].

A key event in inflammation in general, and IBD pathogenesis in particular, is lymphocyte trafficking to the inflammatory sites. This trafficking depends on the interaction between lymphocytes and endothelial cells [18]. Besides chemokines and their receptors, selectins and integrins are among the cell surface molecules involved in lymphocyte endothelial migration into intestinal tissues and have been suggested as important factors mediating tissue injury during acute flares of colitis. Enhanced expression of the adhesion molecules ICAM-1, VCAM-1 and MAdCAM-1 on endothelial cells has been put forth in IBDs. Consequently, adhesion molecule inhibitors targeting lymphocyte trafficking in the intestine have been developed [3,4]. Case in point, Vedolizumab, a recombinant human monoclonal antibody against $\alpha_4\beta_7$-integrin has been used successfully in IBD treatment and other inhibitors of leukocyte trafficking are in clinical development [5].

3. Overview of experimental models of IBD

Several rodent models have been developed in order to study the mechanism of IBDs and investigate therapeutic strategies, including those targeting lipid mediators. While no single experimental model has proven to be an accurate mimic of human IBDs, each model provides valuable insights into different aspects of the disease and the collective data allows for a better understanding of IBD pathogenesis. In these models, either colitis develops spontaneously, is chemically induced or is induced by adoptive transfer of immune cells. Depending on the model, they will mimic either CD or UC more closely with regard to histological features, clinical and immune responses as well as disease location.

Chief among these is the dextran sodium sulfate (DSS) model of colitis. This compound is toxic to colon epithelial cells and therefore inflammation and lesion formation occur via direct epithelial damage leading to the entry of luminal bacteria or bacterial antigens into the mucosa. DSS colitis can be either acute or chronic depending on the dose and frequency of administration of DSS in the drinking water [19]. Inflammation in this model can also develop in the absence of T cells (and thus adaptive immunity) which reinforces the notion that effector cytokines produced by innate cells (such as macrophages and neutrophils) are sufficient to cause inflammation. Thus, this model is crucial to understand the role of innate immune mechanisms in the development of intestinal inflammation.

Other widely used models of chemically induced colitis employ haptenating agents, such as 2,4,6-trinitrobenzene sulfonic acid (TNBS). TNBS is believed to haptenize colonic autologous or microbiota derived proteins rendering them immunogenic to the host which triggers an antigen specific immune response [19]. The clinical findings of the TNBS-induced colitis model are similar to the DSS-induced model, which include bloody diarrhea, weight loss, and epithelial ulceration with inflammatory infiltrate into the lamina propria [19]. However, each disease has distinctive immunologic aspects. Indeed, the TNBS and the acute DSS model are characterized by the predominance of a Th1-Th17 immune response whereas a mixed Th2 immune response was

also put forth in the chronic model of DSS [20]. The use of oxazolone, another haptenating agent, will induce an inflammation driven by natural killer cells that is characterized by a Th2 immune response resembling UC [19].

Mice deficient for the immunomodulatory cytokine IL-10 (IL-10$^{-/-}$) develop colitis spontaneously by 3–4 months of age when housed in conventional environments. However, IL-10$^{-/-}$ germ free mice do not develop spontaneous colitis, which delineates the importance of the gut microbiota in the pathogenesis of colitis. Moreover, the genetic background of IL-10$^{-/-}$ mice determines colitis susceptibility and severity [21]. IL-10 plays a critical role in maintaining homeostasis of the intestinal mucosa by suppressing Th1/Th17 immune responses and therefore IL-10$^{-/-}$ mice mount a heightened Th1 immune response with excessive production of pro-inflammatory cytokines. Interestingly, Th1 cytokines decrease with time in this model while Th2 cytokines increase [19]. Colitis in IL-10$^{-/-}$ mice shows many of the characteristics of human CD including inflammatory infiltrate into the lamina propria and submucosa, transmural inflammatory lesions, epithelial cell hyperplasia, mucin depletion and thickening of the intestinal wall [21]. IL-10$^{-/-}$ mice have also been used to trigger other models of colitis, such as DSS-induced colitis or the adoptive transfer model, in order to study the implication of this cytokine in the model or in the treatments used. The IL-10$^{-/-}$ model has been very useful to study macrophage function and immunoregulation.

The adoptive transfer model of colitis (T-cell transfer colitis) consists of the administration of naïve CD4^{+} T cells from healthy wild type mice to immunodeficient recipients, such as RAG$^{-/-}$ or SCID mice. RAG$^{-/-}$ or SCID mice lack functional mature B and T cells and hence are very immunocompromised [19]. The naïve cells transferred cannot generate regulatory T cells in a timely fashion. Thus, this transfer promotes the expansion of effector T cells that initiate unrelenting inflammatory processes cumulating in CD-like colitis [22]. The predominant response in this model seems to be a Th1-mediated response although Th17 cells are also implicated. This model allows for isolating the function of effector cells and regulatory cells.

Another model for colitis induction is based on the use of anti-CD40 antibodies. CD40 is highly expressed by antigen-presenting cells such as resident dendritic cells in the intestinal lamina propria. The administration of stimulatory antibodies (agonistic anti-CD40) to immunocompromised mice in the anti-CD40 model of colitis triggers the production of pro-inflammatory cytokines by antigen-presenting cells. This causes inflammation to flare up in the colon and the onset of an IBD-like disorder [23]. As this model is developed in Rag$^{-/-}$ mice lacking B and T cells, it is very useful to study the role of innate immunity in colon inflammation.

Collectively, these models show the complexity of IBD pathogenesis and stress the fact that mucosal homeostasis depends on a balance between mucosal pro-inflammatory effector functions and anti-inflammatory regulatory functions. Moreover, most of these models, including the IL10$^{-/-}$ model, do not develop in germ free mice, which highlights the important role played by the microbiota in maintaining colon homeostasis.

4. Bioactive lipids

Lipids perform three main roles in the organism: they are structural components of cell membranes, they act as energy storage and they also function as signaling and regulatory molecules. This last category is termed bioactive lipids (or lipid mediators) [24]. Changes in the concentration of these lipids lead to functional consequences and affect many pathophysiological processes, including inflammation. Bioactive lipids are often formed through enzymatic reactions from lipid

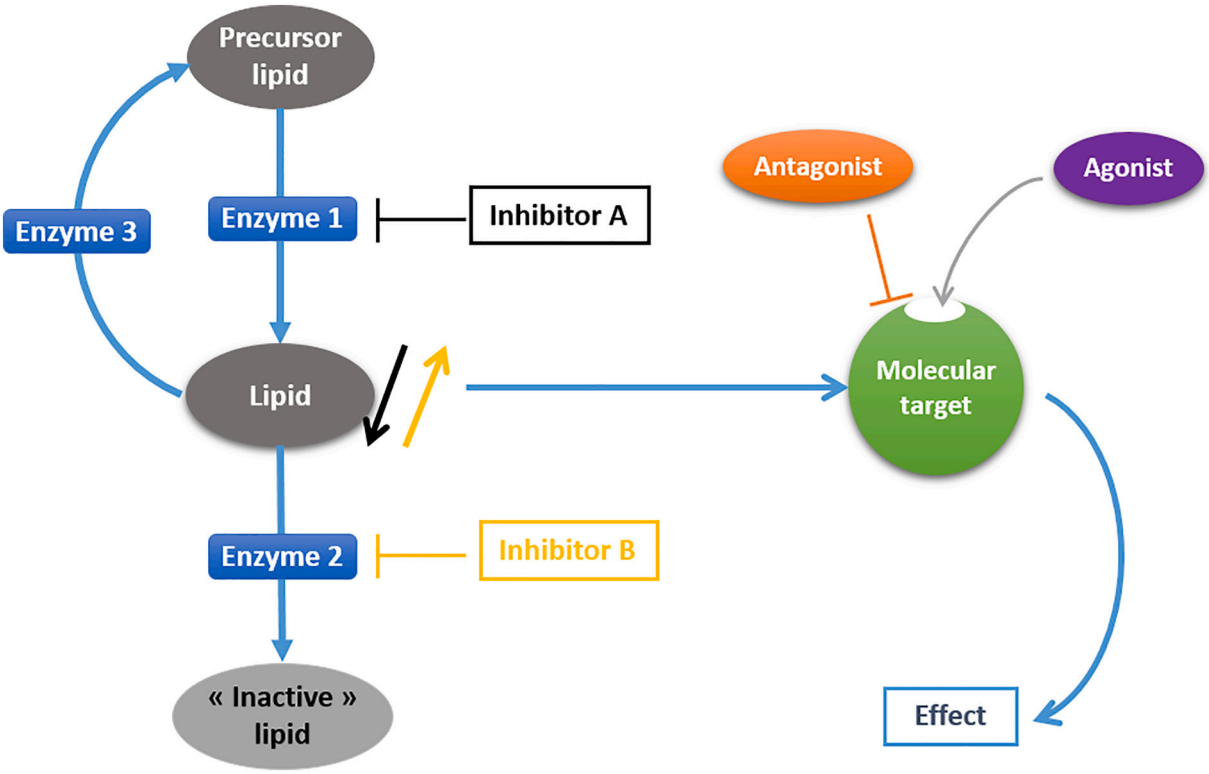

Fig. 1. Schematic representation of bioactive lipid signaling.
Bioactive lipids are typically formed through enzymatic reactions (enzyme 1) from lipid precursors. Their catabolic pathways can include transformation (enzyme 2) into another lipid that does not act on the same targets ("inactive" lipid) or recycling into their precursor lipid (enzyme 3). There are multiple ways of interfering with such pathways: by using agonists or antagonists of the molecular target, to replicate or block the effects, respectively; or by increasing or decreasing the endogenous levels of the lipid of interest by using inhibitors of enzymes 2 or 1, respectively.

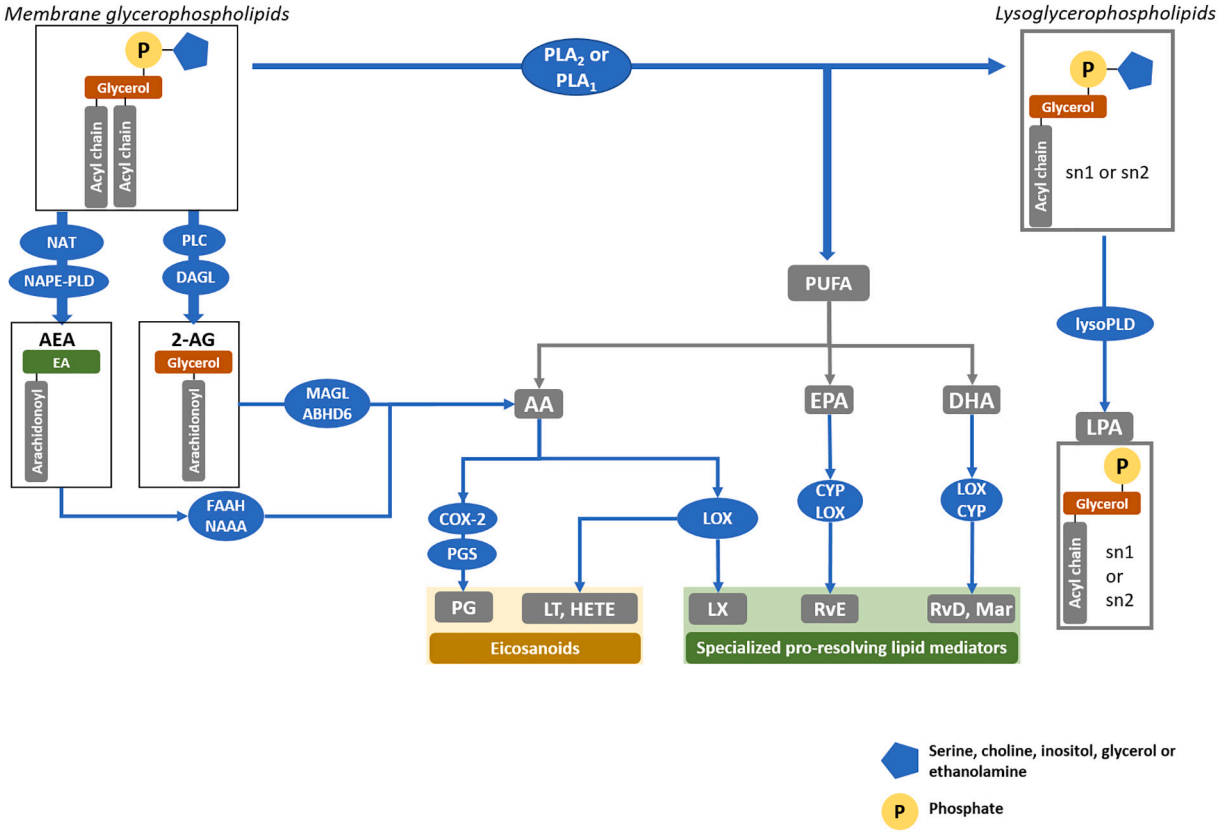

Fig. 2. Simplified metabolic pathway of lysoglycerophospholipids.
Lysoglycerophospholipids are produced from membrane glycerophospholipids via the action of phospholipase A (PLA) enzymes. Depending on the polar head group, different families of lysoglycerophospholipids are formed, such as lysophosphatidylcholines, lysophpsphatidylethanolamines, lysophosphatidylserines, lysophosphatidylglycerols and lysophosphatidylinositols. Hydrolysis of the polar head of lysoglycerophospholipids by a lysophospholipase D (lysoPLD) will produce lysophosphatidic acids (LPA). The most studied lysoPLD for LPA synthesis is Autotaxin.
PLA_2 enzymes are responsible for the hydrolysis of the ester on the sn-2 position of glycerophospholipids, producing sn-1 lysoglycerophospholipids. On the other hand, PLA_1 enzymes will perform the hydrolysis of a sn-1 ester. Besides lysoglycerophospholipids, this activity will release a free polyunsaturated fatty acid (PUFA). Two main forms of PLA_2 are described in cells, the cytosolic PLA_2 ($cPLA_2$) and Ca^{++}-independent PLA_2 ($iPLA_2$). The $cPLA_2$ is selective for phospholipids containing arachidonic acid (AA) in the sn-2 position. On the other hand, $iPLA_2$ is less selective and can release additional fatty acids. PUFA are metabolized by several enzymes such as cyxlooxygenases (COX), lipoxygenases (LOX) and cytochrome P450 (CYP) to give the eicosanoids and specialized proresolving mediators.
AA will lead to the production of prostaglandins (PG), leukotrienes (LT), hydroxyeicosatetraenoic acids (HETE) and lipoxins (LX), among others. Metabolites of docosahexaenoic acid (DHA) include D series resolvins (RvD) and maresins (Mar) while E series resolvins (RvE) are produced from EPA.
The endocannabinoids *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) are released from membrane phospholipids and hydrolyzed by specific hydrolases into AA and ethanolamine (EA) or glycerol, respectively. Other *N*-acylethanolamines not pictured here, such as *N*-palmitoylethanolamine (PEA) for example, are produced and hydrolyzed via the same pathways as AEA and will release ethanolamine and the corresponding fatty acids (palmitic acid in the case of PEA). Endocannabinoids can also be metabolized by the same enzymes as AA to give glycerol ester or ethanolamide derivatives of AA metabolites (not pictured here).
ABHD6: α/β hydrolase domain 6, DAGL: diacylglycerol lipase, FAAH: fatty acid amide hydrolase, NAPE-PLD: *N*-acyl phosphatidylethanolamine phospholipase D, NAT: *N*-acyltransferaese, PGs: prostaglandins, PGS: prostaglandin synthase, PLD: phospholipase D.

precursors. Their catabolic pathways can include transformation into another lipid that does not act on the same targets or recycling into their precursor lipid (Fig. 1). Lipids can control biological processes essentially by interacting with target proteins, typically GPCRs or nuclear receptors, or by altering cell membrane properties. For most bioactive lipids, it is expected that one or multiple molecular targets will mediate the observed biological effects, although the impact of lipid insertion into cell membranes cannot be excluded. Several approaches allow to study the effects of lipid mediators in IBD. The first approach would be to administer the lipid of interest in order to directly assess its effects. However, this does not exclude an impact of the metabolism of this lipid into active or inactive metabolites. Administration of stable analogs or agonists/antagonists of the molecular target(s) (when known) allows to bypass the effect of lipid metabolism. Alternatively, using enzyme inhibitors to increase or decrease endogenous lipid levels would, in theory, benefit from the endogenous lipid signaling pathways.

Bioactive lipids have been implicated in IBDs either following variations in their levels, due to the role of their metabolic enzymes or identified molecular targets, or via genome wide association analysis (GWAS) as we will discuss in the following sections. Owing to the large number of lipid families and species within these families, we will focus on examples of representative lipids (Fig. 2–4) and their role in IBDs to support the interest of interfering with their metabolism and signaling in the context of these diseases.

5. Fatty acids and derivatives

5.1. Fatty acids

5.1.1. Short chain fatty acids

Short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate produced by microbial fermentation, are prime examples of beneficial host-microbiota interactions (Fig. 3 and 4). Decreased SCFA levels have been reported in colon inflammation, both in IBD patients

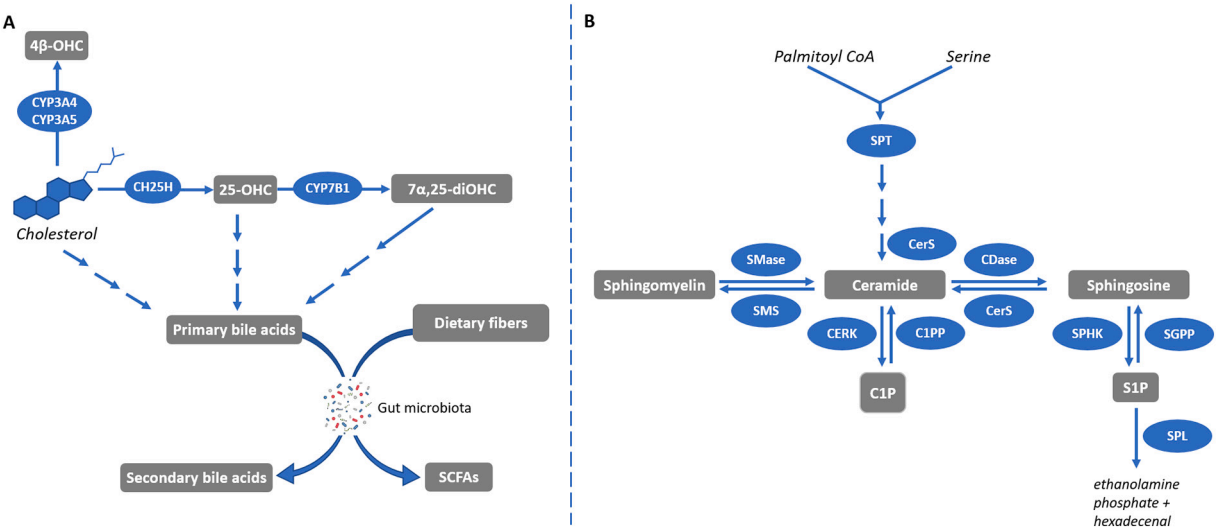

Fig. 3. Simplified metabolic pathways of oxysterols, SCFAs and sphingolipids.
(A) Oxysterols are mainly produced from cholesterol via enzymatic reactions or non-enzymatic processes triggered by reactive oxygen and nitrogen species. Three oxysterols are represented here as illustrative examples of the numerous endogenous oxysterols. 4β-hydroxycholesterol (4β-OHC) is produced by CYP3A4 and CYP3A5 in humans (or their murine orthologs CYP3A11 and CYP3A13). 25-hydroxycholesterol (25-OHC) is primarily produced by the enzyme cholesterol-25-hydroxylase (CH25H) and further metabolized by CYP7B1 into 7α,25-dihydroxycholesterol (7α,25-diOHC). Downstream metabolism of oxysterols will lead to bile acids. Primary bile acids derived from cholesterol metabolism will be further metabolized by the gut microbiota in secondary bile acids. Short chain fatty acids (SCFAs) are also produced by the gut microbiota.
(B) Key reactions involved in the metabolic pathways of sphingolipids. In addition to the de novo synthesis by serine palmitoyl transferase (SPT) followed by ceramide synthases (CerS), ceramides are also generated by the hydrolysis of sphingomyelin by sphingomyelinases (SMase). Ceramides in turn are either hydrolyzed by ceramidase (CDase) into sphingosine or converted into sphingomyelin by sphingomyelin synthase (SMS). Both ceramides and sphingosine are subject to phosphorylation by kinases, ceramide kinase (CERK) and sphingosine kinase (SPHK), to produce ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P), respectively. S1P phosphatases (SPP) and C1P phosphatases (C1PP) respectively convert S1P into sphingosine and C1P into ceramides. S1P Lyase (SPL) converts S1P into ethanolamine phosphate and hexadecenal.

and disease models [25–27] and have been associated with the microbiota dysbiosis observed in IBDs [28]. Moreover, a disruption in SCFA metabolism was put forth following metabolomic profiling of colon biopsies of UC patients compared to controls [29].

Among their many roles, SCFAs are involved in maintaining host tolerance to the commensal microbiota. Indeed, SCFAs were shown to regulate the number and function of colonic Tregs via activation of the free fatty acid 2 receptor (FFA2, also known as GPR43) and inhibition of histone deacetylase (HDAC) [30,31]. They also modulate macrophage function, possibly via HDAC inhibition and modulation of NF-κB activation [32–34], and decrease the release of pro-inflammatory cytokines and chemokines from human monocyte-derived dendritic cells [35]. While some of these effects of SCFAs on macrophages and dendritic cells seem independent of GPCR activation [32], other studies point to a role of GPR109A in this context [36].

SCFAs play a role in the maintenance of epithelial barrier integrity. Indeed, SCFAs, and mainly butyrate, were shown to promote epithelial barrier function in vitro through induction of genes encoding tight junction components and protein reassembly. These effects were mediated by AMPK activation, HDAC inhibition and the activation of transcription factors, such as STAT3 or hypoxia-inducible factor 1 (HIF-1) [37–39]. Production of antimicrobial peptides by intestinal epithelial cells is another mechanism involved in epithelial barrier function. Expression of the antimicrobial peptides Reg3 and β-defensins is strongly impaired in FFA2$^{-/-}$ mice [40]. Accordingly, butyrate and propionate were able to regulate the production of these antimicrobial peptides in a FFA2-dependent manner [40,41].

SCFAs are able to modulate epithelial barrier function by modulating tight junction assembly and antimicrobial peptide production. They are also implicated in the regulation of immune activation in the colon. These elements support a potential beneficial role of SCFAs in IBD.

Consistent with this hypothesis, SCFAs improved T cell–transfer colitis in a IL-10, Treg and FFA2-dependent manner [30,42]. Butyrate was also shown to reduce colitis in a IL-10 independent pathway, via inhibition of HDAC and NF-κB [33]. This SCFA exerted beneficial effects in several studies of acute experimental colitis by decreasing neutrophil infiltration, Th17 cell activation and improving epithelial permeability by preventing tight-junction impairment [27,33,43–46]. Interestingly, while butyrate decreased Th17 cell activation and induced IL-10 expression, it was also shown to promote Th1 cell activation [47]. Perhaps this duality could explain that, in a couple of studies, butyrate did not affect chronic DSS-induced colitis in mice [32] or protect against inflammation-induced loss of epithelial barrier function in vitro and ex vivo [48].

While butyrate has been more widely studied, propionate improved DSS-induced colitis by improving intestinal barrier function and reducing inflammation and oxidative stress [49] and acetate also showed protective effects in DSS-induced colitis with a key role of FFA2, GPR109A and the NLRP3 inflammasome [50,51].

Consistent with experimental models, enema SCFA administration could have some benefits in UC although the reports show varying and inconsistent effects on disease activity [28,34,52]. The discrepancy observed in the clinical studies may be due to differences in treatment duration, use of one or a mixture of SCFAs and the different concentrations and volumes of these mixtures. Future well-powered controlled studies are needed to assess the use of SCFAs as adjuvant therapy in patients with active UC.

5.1.2. *Long chain fatty acids*

Long chain fatty acids are involved in inflammatory processes. Among these, n-6 fatty acids such as arachidonic acid (AA) are classically considered as pro-inflammatory, while n-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are considered as anti-inflammatory and pro-resolving. Indeed, AA metabolism leads to the formation of prostaglandins (PGs) and leukotrienes (LTs) that generally exhibit a pro-inflammatory role, although that is an

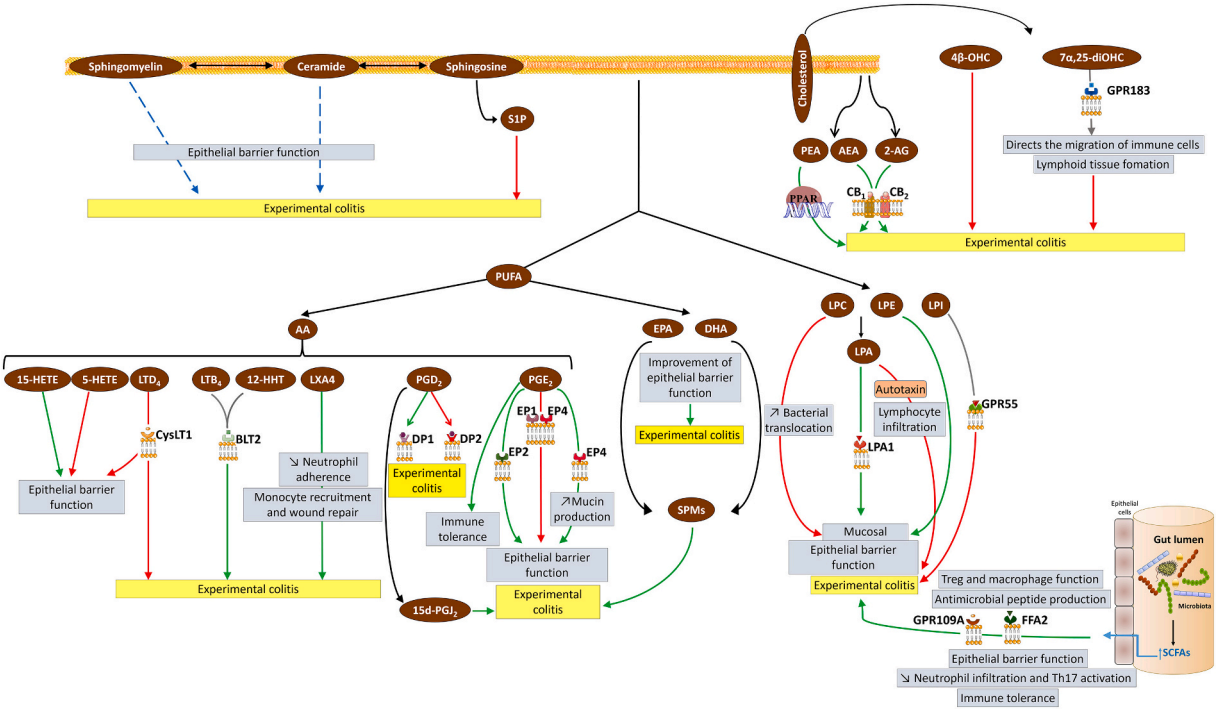

Fig. 4. Summary of the data presented in this review.
In this figure, we summarize some of the data discussed in the review concerning the effects of bioactive lipids in IBD. Black arrows represent enzymatic reactions (with the exception of the spontaneous dehydration of PGD_2 into 15-$dPGJ_2$). Red arrows represent reported deleterious effects while green arrows represent beneficial effects in in vitro or in vivo experimental models of IBDs. The effects of lipid receptors on IBDs was often put forth using pharmacological modulators or receptor knockout. Details on whether the lipids were administered or whether receptors have been invalidated/inhibited are described in the text. For instance, in some cases the effect of a receptor was studied in IBD models but the effect of the endogenous ligand was not demonstrated (e.g. 12-HHT or LPI). The data for sphingolipids is conflicting (with the exception of S1P) as summarized in the review, and are thus represented with the blue dashed arrows.

oversimplification of their roles in inflammation. EPA also leads to the production of PGs and LTs, but these are believed to be less pro-inflammatory than the AA-derived PGs and LTs [53]. Moreover, EPA and DHA are precursors of most specialized pro-resolving lipid mediators (SPM), including resolvins, protectins, and maresins, while lipoxins are derived from AA.

Following metabolomic profiling of colon biopsies of UC patients compared to controls, pathway analysis showed a disruption in the metabolism of long-chain fatty acids [29]. Moreover, a higher concentration of AA and a lower concentration of EPA were found in the inflamed colonic mucosa of UC patients [54]. In another study, the n-6/n-3 ratio was found to be elevated in the rectal mucosa of IBD patients compared to controls [55]. In light of these data, a disruption of the dietary n-6/n-3 fatty acid ratio could favor ongoing inflammation. Consistent with this hypothesis, the "western diet" was associated with an increased risk of IBDs [56]. Accordingly, in prospective studies, dietary n-6 fatty acids were positively correlated with UC risk, while dietary n-3 fatty acids showed a negative association [57–60].

Benefits of n-3 supplementation were put forth in murine models of IBD. Indeed, in rats with TNBS-induced colitis, nutritional intervention with n-3-rich formula decreased colon inflammation, oxidative stress and eicosanoid production [61,62]. Dietary intervention with n-3 rich fish oil also triggered a reduction of VCAM-1 and VEGFR2, which would inhibit neutrophil transepithelial migration [63]. Moreover, supplementation with DHA reduced colitis severity and inflammation in the $IL10^{-/-}$ model of colitis [64] and improved epithelial barrier function by rescuing the expression and distribution of occludin and ZO-1 [64]. Besides n-3 administration, the use of a n-6/n-3 balanced diet or of genetic mouse models where n-6 synthesis is reduced also attenuated colon inflammation in experimental models of colitis, along with decreased Th17 cell activation [65,66]. These studies further stress the need to balance the n-6/n-3 ratio as dietary intervention in IBD. However, although data from rodent studies appear promising, nutritional intervention studies with n-3 fatty acids have not shown clear beneficial effects in IBD patients [67,68]. Surprisingly, an enteral diet high in n-6 fatty acids induced clinical remission in patients with active CD, thus suggesting that n-6 fatty acids do not only have pro-inflammatory effects [69].

Besides being precursors for eicosanoids and SPMs (see next sections), fatty acids can bind nuclear and membrane receptors that serve as dietary lipid sensors and have been implicated in IBDs [70]. DHA can activate the peroxisome proliferator-activated receptors (PPAR), as well as the retinoid X receptor (RXR) and the farnesoid X receptor (FXR). These receptors are known to exert anti-inflammatory effects and are involved in colon homeostasis [70]. For instance, PPARγ has been identified as a susceptibility gene in CD and its expression was reduced in colon biopsies from UC patients [71,72]. Accordingly, PPARɣ and RXR were shown to have beneficial effects in TNBS-induced colitis in mice [73]. Linoleic acid, an n-6 fatty acid and the dietary precursor of AA, is also a ligand of the PPAR receptors. Linoleic acid also binds the transcription factor hepatocyte nuclear factor 4-α (HNF4-α). HNF4-α expression was decreased in colon biopsies from IBD patients and in DSS-induced colitis in mice [74,75]. This transcription factor exerts protective effects in DSS-induced colitis [75]. Linoleic acid, AA, DHA and EPA are also ligands of the GPCRs FFA1 (GPR40) and FFA4 (GPR120), which have been recently suggested to decrease inflammation in murine colitis models [76,77]. Therefore, while it seems important to increase nutritional intake of n-3 fatty acids, n-6 fatty acids could also exert beneficial effects in inflammatory settings and should not be completely shunned.

5.2. *Fatty acid derivatives*

Inflammatory cells, among others, produce a variety of lipid

mediators that have been implicated in inflammation in general and IBDs in particular. The most studied of these lipid mediators are the eicosanoids such as PGs, thromboxanes (TXs), and LTs derived from AA, through the actions of cyclooxygenases (COX) and lipoxygenases (LOXs). AA is released from membrane phospholipids through the action of the phospholipase A_2 (PLA_2) enzymes, which have been implicated in IBD pathogenesis [78]. Inhibition of the enzymes producing these lipid mediators has been widely used as anti-inflammatory strategy because these lipids are broadly considered as pro-inflammatory mediators. However, it is increasingly clear that some of these lipid mediators exert beneficial effects depending on the settings. Moreover, LOX enzymes also produce other lipid mediators such as the SPMs (Fig. 2).

5.2.1. Prostanoids, leukotrienes and epoxyeicosatrienoic acids

PGs are usually produced in low levels by COX-1, the constitutively expressed isoform of COX, and exert homeostatic functions such as gastric epithelial cytoprotection. Because COX-2 can be induced by pro-inflammatory stimuli and cytokines, the levels of PGs increase dramatically during an inflammatory response. The profile of PG production in a given tissue is dependent on the differential expression of the thromboxane synthase and PG synthases. The importance of prostanoids in the promotion of pain, fever and inflammation is clear when considering the clinical efficacy of COX inhibitors. However, PGs clearly function in both a homeostatic and inflammatory capacity and COX inhibitors could exert detrimental effects in IBDs and experimental models [79–82]. In mice with lipopolysaccharide-induced systemic inflammation, COX inhibition increased the gut epithelial permeability, leading to bacterial translocation to the blood and tissues [83]. This data suggests beneficial effects for COX-derived eicosanoids in IBD.

Among the prostanoid receptors, the PGE_2 receptor EP4 was identified in a GWAS study as a disease susceptibility gene in CD [84]. This receptor was constitutively expressed in the colonic epithelium and its expression was increased in experimental models of IBDs [82,85]. PGE_2 levels were increased in the inflamed mucosa of IBD patients [86,87] and in the acute phase of DSS-induced colitis in mice, but not in the recovery phase [88,89]. Moreover, a negative correlation was suggested between mucosal PGE_2 levels and disease severity in DSS-induced colitis [90].

Overall, PGE_2 seems to exert beneficial effects in IBD, although conflicting observations are sometimes reported. For instance, in vitro, EP1 and EP4 activation by PGE_2 was shown to disrupt the epithelial barrier function via redistribution of tight junction proteins such as occludin and the peri-junctional actin ring [91,92]. Conversely, EP4 activation by PGE_2 induced mucin gene transcription and mucin exocytosis in epithelial cells, which would suggest a protective role [93,94]. Moreover, the EP2 receptor was shown to maintain epithelial barrier integrity by controlling claudin-4 degradation [95]. Consistent with this protective role, PGE_2 was also shown to act on type 3 innate lymphoid cells, drive IL-22 production and improve gut-leakage in a model of systemic inflammation in mice [83]. Interestingly, this PG also seems to play an essential role for maintenance of immune tolerance in the intestine along with suppressor of cytokine signaling 1 (SOCS1) [96].

In vivo studies in colitis models support a beneficial effect of PGE_2, although some detrimental effects can be observed, especially when using EP receptor agonists. This is probably due to the different EP receptors activated depending on the molecule used. For instance, administration of misoprostol (an EP2, EP3 and EP4 agonist) worsened TNBS-induced colitis in mice by increasing neutrophil infiltration in the colon and promoting Th17 cell differentiation [81]. However, several studies reported beneficial effects of the EP4 receptor in vivo [82,97]. Indeed, $EP4^{-/-}$ mice or mice receiving an EP4 antagonist showed increased susceptibility to DSS-induced colitis and implicated this receptor in the maintenance of the mucosal barrier function and the regulation of immune responses [82], while EP4 agonists improved experimental colitis [82,85]. An EP4 agonist (ONO-4819) was successfully used in a phase-II clinical trial and showed histological improvement of UC, although the sample size was quite small (4 patients receiving the treatment and 3 receiving placebo) [98].

PGD_2 seems to generally exert beneficial effects in the colon, although, again, this depends on the receptor considered. PGD_2 levels were increased both in the inflamed mucosa of IBD patients and in biopsies from UC patients in remission [99]. The expression of the DP1 receptor was increased both in experimental models of IBDs [82] and in biopsies from UC patients in remission [99]. Decreasing PGD_2 production via genetic deletion of hematopoietic prostaglandin D synthase (HPGDS) worsened DSS-induced colitis in mice while administration of a DP1 receptor agonist improved colon inflammation [100]. Using receptor antagonists, it was shown that the DP1 receptor exerted beneficial effects in DSS-induced colitis, while the DP2 receptor was detrimental [101]. PGD_2 and its metabolite 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2) have also been suggested to play a role in the resolution of inflammation [102]. 15d-PGJ_2 is a PPARγ agonist, however, it was recently shown to improve DSS-induced colitis via a PPARγ-independent mechanism that involved induction of heme oxygenase-1 [103].

Less is known about the effects of LT and other COX and LOX products in IBD, as few studies have addressed their role in this setting. High levels of LT were detected in the urine and colonic mucosa of IBD patients [87,104] and in the acute phase of DSS-induced colitis in mice [88]. It was suggested that the LOX pathway could also be involved in the regulation of tight-junction permeability. LTD_4 and 5-HETE altered the epithelial permeability in vitro. This effect was via the CysLT1 receptor for LTD_4 and via an unknown mechanism for 5-HETE [105]. Accordingly the CysLT1 antagonist montelukast improved experimental colitis [106]. However, 15-HETE, another LOX product was shown to exert beneficial effects on epithelial barrier permeability in vitro by increasing ZO-1 expression, and its levels were reduced in enteric glia cells from CD patients [107]. 12-Hydroxyheptadecatrienoic acid (12-HHT), a product of COX and thromboxane synthase, was implicated in the maintenance of epithelial homeostasis and the promotion of wound healing [108]. Deletion of its receptor BLT2 worsened experimental colitis [109]. This receptor was also proposed as a receptor for LTB_4, but 12-HHT was shown to be the most potent endogenous agonist of this receptor [110].

Besides COX and LOX enzymes, AA can be metabolized by CYP450 enzymes, mainly CYP2J2, to produce epoxyeicosatrienoic acids (EET). These EETs exert anti-inflammatory effects in several in vitro and in vivo models [111]. CYP2J2 was shown to be involved in bacterial phagocytosis by macrophages [112]. Moreover, while *Escherichia coli* induced CYP2J2 in macrophages from healthy donors, this was not the case for macrophages from CD patients. As bacterial clearance is altered in IBD, this could implicate CYP2J2 in CD pathogenesis [112]. Consistent with the anti-inflammatory effects of EETs, inhibition of soluble epoxide hydrolase (sEH), the enzyme responsible for their hydrolysis, is considered as an anti-inflammatory strategy [111]. This is also the case in colitis models where pharmacological inhibition or genetic deletion of sEH exert anti-inflammatory effects [113–115]. These studies put forth EETs as anti-inflammatory lipid mediators in IBDs and suggest a role for sEH in IBD pathogenesis. Furthermore, this reinforces the notion that AA-derived lipid mediators can exert both anti- and pro-inflammatory effects, which depend on the mediator and the setting.

5.2.2. Specialized pro-resolving mediators

Generally, SPMs inhibit neutrophil infiltration, promote phagocytosis of apoptotic neutrophils and the phenotypic switch of macrophages, which leads to decreased inflammation and promotes homeostasis. The chronic inflammation in IBDs could be considered as a failure of resolution. Therefore, these lipid mediators and their receptors merit further exploration as novel therapeutic options for IBD treatment.

Impaired lipoxin biosynthesis was found in colonic mucosa from UC patients [116] and lipoxin A4 (LXA_4) levels were increased in the mucosa of UC patients in remission, along with increased macrophage

infiltration, and increased mRNA of its receptor formyl peptide receptor 2 (FPR2/ALX) [117]. LXA_4 levels were also found to be negatively correlated with histopathologic alterations in experimental colitis, suggesting a beneficial role for this SPM in this setting [118]. Accordingly, administration of a LXA_4 analog (15-epi-16-para-fluoro-phenoxy-LXA_4) improved DSS-induced colitis in mice [119]. LXA_4 also inhibited TNF-α-stimulated neutrophil adherence to epithelial monolayers in vitro [120] and TNF-α-stimulated release of IL-8 and MCP-1 from human colonic mucosa ex vivo [120]. LXA_4 and its analogs exert their effects by decreasing NF-κB-mediated transcriptional activation via activation of the FPR2 receptor [119]. This receptor was suggested to facilitate monocyte recruitment to sites of mucosal injury to promote wound repair [121].

Altered levels of several other SPMs were also found in biopsies from CD patients and in the colon of mice with DSS-induced colitis [87]. Protectin D1 (PD1) levels were increased in the colon of mice with DSS-induced colitis and decreased in colonic tissue of eosinophil-deficient mice that develop more severe acute colitis compared to control mice [87,122]. Accordingly, administration of an exogenous PD1-isomer ((10*S*,17*S*)-DiHDoHE) reduced neutrophil infiltration and inflammatory markers, thus reducing DSS-induced colitis severity in eosinophil-deficient mice [122].

The EPA-derived resolvin E1 (RvE1) showed beneficial effects in TNBS- and DSS-induced colitis in mice, through ChemR23 receptor activation and subsequent inhibition of NF-κB nuclear translocation [123,124]. Some of the effects of RvE1 in DSS-induced colitis were mediated by intestinal alkaline phosphatase (ALPI), an enzyme involved in lipopolysaccharide detoxification [125]. Other SPMs such as aspirin-triggered resolvin D1 (AT-RvD1), its precursor (17*R*)-hydroxydocosahexaenoic acid, resolvin D2 (RvD2) and maresin-1 (Mar1) also showed beneficial effects in acute and chronic experimental colitis [126–128]. The decreased colon inflammation was accompanied by decreased expression of adhesion molecules, leading to decreased neutrophil infiltration and a decrease in macrophage infiltration [126–128]. The effects of AT-RvD1 were mediated by the FPR2 receptor [126], while the effect of Mar1 on acute colitis was mediated through signaling via the nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that plays a key role in antioxidant and inflammatory responses and protects against oxidative stress [129].

Generally, the effects of SPMs on intestinal inflammation are related to a reduction of NF-κB transcriptional activation, a decrease in neutrophil infiltration and the phenotypic switch of macrophages [87,119,122,124,128]. Further reinforcing the beneficial effects of SPMs in IBD models is the modulation of their endogenous levels. Indeed, the use of 15-LOX inhibitors (e.g. PD146176), which inhibit SPM production, worsened DSS-induced colitis in mice while administration of aspirin, which increased the levels of LXA4 and 17-HDHA, decreased colon inflammation in this setting [87,116,130]. These studies suggest a central role of SPMs in colitis. Although several receptors have been identified for the SPMs, the implication of these receptors in this context has not been studied so far. Assessing the involvement of SPM receptors in the intestinal immune-regulatory response could point to new therapeutic avenues to be investigated using stable agonists of these receptors for IBD treatment.

6. Endocannabinoids and related lipids

Endocannabinoids are bioactive lipids that bind and activate the cannabinoid receptors CB_1 and CB_2, two G protein-coupled receptors. The two most studied endocannabinoids are *N*-arachidonoylethanolamine (AEA), an *N*-acylethanolamine (NAE), and 2-arachidonoylglycerol (2-AG). They are produced from membrane phospholipids and their actions are terminated following their hydrolysis by specific lipases. The biosynthetic pathway of 2-AG involves a phospholipase C that releases diacylglycerols (DAGs) from phospholipids followed by the action of diacylglycerol lipases (DAGL). 2-AG is hydrolyzed by several hydrolases, namely monoacylglycerol lipase (MAGL) and α/β-hydrolase domain (ABHD) 6 and 12, into AA and glycerol. There are multiple synthetic pathways for AEA but the most studied involves an *N*-acyltransferase that produces *N*-acylphosphatidylethanolamines (NAPEs) and a NAPE-preferring phospholipase D (NAPE-PLD) that removes the phosphate group to give NAEs. *N*-palmitoylethanolamine (PEA) and *N*-oleoylethanolamine (OEA), as well as other NAEs, share the same metabolic pathways as AEA. NAEs are hydrolyzed by two amidases, fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine acid amidase (NAAA) into ethanolamine and a fatty acid [131].

Endocannabinoids and related NAEs exert numerous effects in the gastrointestinal tract, ranging from the regulation of food intake to the modulation of inflammation and intestinal permeability [132]. The levels of AEA and other NAEs were shown to be altered in colon biopsies from IBD patients, especially during acute flares, while the levels of 2-AG remained unchanged [133–135]. However, depending on the study, NAE levels were increased or decreased. Similarly, in experimental models of colitis, AEA levels were altered with no change in 2-AG levels. Interestingly, AEA levels seem to be differentially regulated in the different colon structures [134].

Consistent with the hypothesis of anti-inflammatory effects of the endocannabinoids in IBD, mice deficient for the CB_1 or CB_2 receptors exhibit increased susceptibility to experimental colitis [136,137] while $FAAH^{-/-}$ mice are protected [136]. Interestingly, a single nucleotide polymorphism in the CB_1 gene was associated with UC susceptibility and CD phenotype [138] while a single nucleotide polymorphism in the FAAH gene was associated with severe disease phenotype in CD [139]. Accordingly, NAE administration [140–142] or increasing endogenous NAE levels by inhibiting FAAH or NAAA resulted in a decrease of colon inflammation in murine models [143–146]. Some of the effects of enzyme inhibition were dependent on AEA and cannabinoid receptor activation while others were due to other NAEs such as PEA, which is a PPARα ligand [140,141,143,144].

Moreover, while 2-AG levels were unchanged in colon biopsies, an increased turnover of this bioactive lipid was put forth [147]. Accordingly, inhibition of MAGL increased 2-AG levels in the colon and counteracted TNBS-induced colitis [148]. Furthermore, studies using cannabinoid receptor agonists further strengthened the potential of the endocannabinoid system as a therapeutic target in IBDs [147,149].

The studies briefly outlined here support a role for the endocannabinoid system and related lipids in IBD. However, many pathways remain to be explored in the endocannabinoid system. For instance, the oxidative metabolism of endocannabinoids by COX, LOX or CYP450 enzymes further opens up new pathways to be investigated [131]. Indeed, the products of this metabolism are emerging as bioactive lipids in their own right with anti-inflammatory properties, including in murine models of IBDs [131,150]. Moreover, several NAEs that remain poorly studied, such as *N*-docosahexaenoylethanolamine (DHEA) or *N*-eicosapentaenoylethanolamine (EPEA), were shown to decrease macrophage activation and exert anti-inflammatory properties [234,235]. Whether they also have beneficial effects in IBDs and are implicated in the observed therapeutic benefits of inhibition of NAE hydrolysis remains to be studied.

7. Lysoglycerophospholipids

Lysoglycerophospholipids consist of a phosphoglycerol backbone, an acyl chain on the sn-1 or sn-2 position and a head group that determines the lysophospholipid family, for example choline for lysophosphatidylcholines (LPC) or ethanolamine for lysophosphatidylethanolamines (LPE). These lysophospholipids are released from membrane glycerophospholipids through the actions of PLA_1 or PLA_2 enzymes (Fig. 2). PLA_2 enzymes catalyze the hydrolysis of the fatty acyl ester bond at the sn-2 position of glycerophospholipids to produce free fatty acids and the corresponding lysoglycerophospholipid, while PLA_1 enzymes cleave at the sn-1 position resulting in the sn-2 isomer. The resulting

lysoglycerophospholipids can be further cleaved by a lysophospholipase D (LysoPLD) to give lysophosphatidic acids (LPA) that are devoid of a polar head group. Lysoglycerophospholipids can also be reacylated into phospholipids via enzymatic reactions [151].

When studying IBDs and the role of PLA_2 enzymes in this context, the focus has been on the fatty acids and their derivatives (see above), however, an increasing number of reports support the interest of studying the properties of lysoglycerophospholipids [151,152]. Among the lysoglycerophospholipids that have been studied in IBDs are the LPA, LPC and LPE.

LPA are easily among the most studied lysoglycerophospholipids in inflammation and immune responses. They have been shown to modulate innate immunity by inducing monocyte transformation into macrophages and promoting an M1 phenotype [153,154]. Moreover, LPA exert chemokinetic effects that induce lymphocyte migration [155]. These reported effects of LPA on immune cells could point to a deleterious effect of LPA in IBD. This is the case when interfering with LPA metabolism by inhibiting the lysoPLD autotaxin, one of the most described enzymes for LPA synthesis and the major contributor to extracellular LPA. Indeed, autotaxin can bind to lymphocytes in a α4β1-dependent manner and enhance lymphocyte migration into secondary lymphoid tissues [155].

Autotaxin expression is increased in inflamed areas from colon biopsies of patients with IBDs and in the colon of mice with T cell-transfer colitis or chronic DSS-induced colitis [156,157]. This increase leading to LPA production is accompanied by increased MAdCAM-1 expression and increased lymphocyte infiltration in the mucosa [156,157]. Accordingly, autotaxin inhibition or deletion decreased MAdCAM-1 expression, lymphocyte infiltration and cytokine expression and improved colitis in several murine models [156–158]. Therefore, the autotaxin-LPA axis seems to be implicated in the pathogenesis of IBD. Autotaxin inhibitors could therefore prove useful as potential therapies in this context. Moreover, the autotaxin-LPA axis has also been implicated in fibrosis development [159], although this has not been investigated in the context of the colon.

However, contrary to what is observed with autotaxin inhibition and suggested by the reported effects of LPA on immune cells, several studies suggest beneficial roles for LPA in the gut. Indeed, LPA was shown to regulate fluid absorption in epithelial cells and reduce diarrhea [160,161]. Moreover, early studies with LPA showed enhanced wound healing in vitro and decreased mucosal damage in vivo in rats with TNBS-induced colitis [162,163]. LPA exert their effects through 6 GPCRs, termed $LPA_{1–6}$, with LPA_1 and LPA_5 being the most expressed in the rodent colon [160]. Accordingly, genetic ablation or pharmacologic inhibition of LPA_1 impaired topical wound healing in the colon, increased epithelial permeability and bacterial translocation and exacerbated DSS-induced colitis [164,165]. These results implicate LPA_1 in the maintenance of epithelial barrier homeostasis and stress the need to dissect the receptor-dependent effects of LPA.

Compared to LPA, less is known for other lysoglycerophospholipids in the context of IBD. Variations of LPC levels in IBDs and murine models have not been consistent. Indeed, colon LPC levels were decreased in murine models of IBDs [166] but were increased in colon biopsies of patients with UC compared to controls [29]. However, when looking specifically at the mucus layer, phosphatidylcholine (PC) and LPC were decreased in the mucus layer of patients with UC compared to CD or controls, with a higher LPC to PC ratio [167,168]. As PC are by far the most abundant phospholipid species in the mucus, the decrease in PC can contribute to the altered epithelial permeability and increase in bacterial translocation found in IBD. Actually, PC was found to decrease bacterial translocation in vitro, while LPC increased epithelial barrier permeability and bacterial translocation [169]. However, the differential alterations in LPC levels between the mucus and the mucosa could point to different roles of LPC at the mucus level and at the tissue level.

A role of LPE in IBDs was suggested a couple of decades ago when it was shown that intrarectal administration of LPE reduced inflammation and mucosal damage in TNBS-induced colitis in rats [163]. More recently, the implication of LPE in IBDs was strengthened in a nice example of the crosstalk between the microbiota and the host via lipid mediators. Zou et al. showed that a SNP of *E. coli blc* gene decreases LPE storage in this bacterium [170]. Accordingly, a disruption of the intestinal epithelial barrier leading to colon inflammation was observed in mice infected with *E. coli* carrying the SNP variant of blc, along with a decrease in LPE 18:1 in mice feces [170]. Oral supplementation of LPE 18:1 normalized ZO-1, occludin, and claudin-1 expression and rescued the intestinal permeability defects [170]. Interestingly, LPE 16:0 and LPE 18:1 levels were decreased in faecal samples from patients with UC compared with those from controls [170].

Little is known about the effects of other lysoglycerophospholipids such as lysophosphatidylserines or lysophosphatidylinositols (LPI) in IBD, despite their implication in inflammatory processes. For instance, lysophosphatidylserines could play a potential role in the resolution of inflammation [171]. GPR132 (also known as G2A), a proposed receptor for lysophosphatidylserines [171], could exert beneficial effects in IBD. Indeed, knockout of this receptor worsened DSS-induced colitis in mice [172]. However, this receptor was also reported to be activated by 9-hydroxyoctadecadienoic acid (9-HODE) and other oxidized fatty acids, and was proposed as a proton-sensing receptor [173,174]. Therefore, the implication of lysophosphatidylserines in this context remains to be investigated. This is also the case for LPI as they have been implicated in several pathophysiological processes including inflammation but not IBD [151]. Antagonism or knockdown of their receptor GPR55 ameliorated experimental colitis in mice, suggesting a pro-inflammatory role for these lipids [175].

Lysoglycerophospholipids constitute a typical example of bioactive lipids that have been overlooked in some regard and have been mainly considered as membrane constituents. Furthermore, these lipids exemplify the complexity that is often encountered when studying lipid mediators, their metabolism and their targets. Indeed, the metabolic pathways of lysoglycerophospholipids are very redundant and interfering with one enzyme could affect the levels of several of these bioactive lipids. For instance, autotaxin inhibition is used to decrease LPA levels but it could also affect the levels of the upstream lysoglycerophospholipids. This could perhaps explain the discrepancies observed between direct administration of LPA and autotaxin inhibition. Moreover, in the case of LPA, several receptors have been described and they do not mediate the same effects, therefore identifying the molecular targets mediating a specific effect is crucial to identify potential pathways of interest in specific pathologies. Finally, an important notion to consider when looking at the effects of lysoglycerophospholipids is that often authors refer to LPA or LPC (or others) as a single lipid, however, there are several species of each family of lysoglycerophospholipids that differ by the fatty acyl chain and it is not always clear whether a mixture of species or a single species (and which one) has been used in in vitro or in vivo experiments.

8. Oxysterols

Oxysterols are oxygenated derivatives of cholesterol that can be either produced endogenously or ingested in the diet. Cholesterol can be oxidized both on the sterol moiety and on the side chain. These oxidation reactions occur either through enzymatic reactions or non-enzymatic processes triggered by reactive oxygen and nitrogen species. CYP450 enzymes constitute the main enzyme family involved in cholesterol oxidation into oxysterols (Fig. 3A). Oxysterols can undergo further transformations. For instance, cholesterol can be hydroxylated in the C25 position by the enzyme cholesterol-25-hydroxylase (CH25H) to form 25-OHC which can be further metabolized by the sulfotransferase 2B1b (SULT2B1b) and CYP7B1 into 25-hydroxycholesterol-3-sulfate (25-OHC-3-sulfate) or into 7α,25-dihydroxycholesterol (7α,25-diOHC), respectively. In turn, 7α,25-diOHC can be further converted by the hydroxysteroid dehydrogenase (HSD) 3B7 or by other CYP450 enzymes

into bile acids. 4β-hydroxycholesterol is formed by CYP3A4 and CYP3A5 and undergoes a second hydroxylation by CYP27A1, CYP7A1 and CYP46A1 to form 4β,27-dihydroxycholesterol (4β,27-diOHC), 4β,7-dihydroxycholesterol (4β,7-diOHC) or 4β,24-dihydroxycholesterol (4β,24-diOHC) respectively [176].

First known as intermediates and end products of the metabolic pathway of cholesterol, oxysterols are now increasingly studied as bioactive lipids with broad roles in physiological processes and pathological disorders. Indeed, oxysterols have been proposed to act as modulators of immune responses, including macrophage activation, immune cell trafficking, Th cell differentiation, inflammasome activation and cytokine production [177]. Therefore, they could play a role in IBD. Actually, oxysterol metabolism was shown to be altered in IBD, both in colon biopsies of patients with CD or UC and in acute and chronic murine models of colitis [178,179]. Among the oxysterols quantified, 25-OHC and 7α,25-diOHC were increased. Accordingly, mRNA expression of CH25H and CYP7B1 was also increased both in mice and in colon biopsies of patients with IBDs [178]. A correlation between their expression and disease severity was also observed [180]. Moreover, CH25H expression was correlated with markers of intestinal fibrosis in samples from CD patients and mice deficient for CH25H exhibited reduced intestinal fibrosis upon chronic DSS administration [181]. However, the severity of DSS-induced colitis was not affected by the administration of 25-OHC [179] or by knockout of CH25H [178]. On the other hand, 4β-OHC was increased in murine models of colitis and decreased in colon biopsies of CD and UC patients [179]. Administration of 4β-OHC exacerbated colon inflammation [179]. Despite their potential as immune modulators, only a few studies investigated the effects of a direct administration of oxysterols, or of interfering with their levels, in IBD. Therefore, further studies are needed to decipher the role of the various oxysterols in IBD. Indeed, there are many oxysterol species besides the ones reported here that could be implicated in colon inflammation. Oxysterol receptors on the other hand have been more studied.

Among oxysterol receptors, GPR183 and liver X receptors (LXRs) were identified as IBD risk genes by GWAS [182,183]. GPR183 is a receptor expressed on immune cells and was shown to be highly expressed by type 3 innate lymphoid cells [13,180]. Oxysterol sensing by this receptor, of which 7α,25-diOHC is a potent ligand, directs migration of immune cells [177]. A single nucleotide polymorphism in GPR183 was shown to increase the risk of both CD and UC [182]. This receptor is involved in the migration of innate lymphoid cells and it was shown that GPR183 and 7α,25-diOHC are essential for lymphoid tissue formation in the colon [178,180]. Moreover, GPR183 expression is increased in mice with colitis and in colon biopsies of UC patients [178]. As lymphoid tissues are critical for the development and persistence of colon inflammation, this points to a role for GPR183 in IBD pathogenesis. Accordingly, GPR183 knockout improved colitis in the IL10$^{-/-}$ spontaneous model of colitis [178] and in CD40 antibody-induced colitis in Rag$^{-/-}$ mice [180]. However, this was not the case in acute or chronic DSS-induced colitis [178]. Why GPR183 affects colitis in certain models and not others remains to be investigated, although this could be due to the characteristics of each model and the cells involved. Indeed, as explained previously, in DSS-induced colitis, the primary defect is a breakdown in the intestinal epithelial barrier and the subsequent activation of the innate immune system, whereas IL-10$^{-/-}$ colitis is due to a lack of immunoregulatory effects of IL-10 on various cell types. The CD40 antibody-induced colitis highly depends on innate lymphoid cells due to the deficiency of B and T cells in Rag$^{-/-}$ mice.

Several oxysterols have been reported as LXR ligands, although their effects on LXRs during IBDs have not been investigated. Among their many effects, LXRs are known as anti-inflammatory transcription factors that regulate immune responses [184]. For instance, LXR activation was shown to decrease Th1 and Th17 differentiation and induce Treg differentiation [185]. Polymorphisms in LXRs have been linked to increased IBD risk [183] and expression of both LXRα and LXRβ was decreased in colon biopsies of patients with UC and CD [179,186]. Accordingly, LXR deficient mice showed an increased susceptibility to DSS-induced and TNBS-induced colitis while a synthetic LXR agonist showed beneficial effects in DSS-induced colitis [186].

Although administration of oxysterols does not conclusively establish their implication in IBD, their receptors clearly play a role in disease progression and the data so far implicates the GPR183-7α,25-diOHC axis in IBD pathogenesis. However, despite the evidence showing beneficial effects for LXRs in intestinal inflammation, the role of oxysterols as LXR modulators remains unclear in this setting. Besides LXRs and GPR183, RAR-related orphan receptors (ROR) α and γ and the estrogen receptor (ER)α are also proposed oxysterol receptors [176]. And while these receptors have been somewhat neglected in IBD research, ERα and RORα have been recently implicated in the maintenance of intestinal homeostasis and their activation alleviates DSS-induced colitis [187,188]. Conversely, RORα-dependent functions of type 3 innate lymphoid cells were also implicated in the development of fibrosis in CD [189]. Moreover, RORγ, and to a lesser extent RORα, are signature transcription factors that control the expression of key Th17 genes [190,191]. Given the implication of innate lymphoid cells and Th17 cells in autoimmune diseases, including IBD, antagonists or inverse agonists of these transcription factors could exert beneficial effects in IBDs [190,192]. Several CYP27A1-derived oxysterols, such as 7β,27-diOHC, are agonists of RORγ and were shown to drive Th17 differentiation [193]. Whether oxysterols affect IBDs through these pathways and receptors remains to be studied.

As mentioned, several oxysterols are intermediates of the biosynthetic pathway of bile acids from cholesterol. Bile acids can activate several receptors such as FXR, the vitamin D receptor or the transmembrane G protein-coupled receptor 5 (TGR5), among others, and exert metabolic and immune effects. These receptors have been shown to exert beneficial effects in experimental models of IBDs [70]. Bile acids are also a prime example of the two-way interaction between the host and the microbiota. Indeed, primary bile acids can be converted by the microbiota into secondary bile acids (Fig. 3) and bile acids can influence microbiota composition. Accordingly, altered bile acid profiles have been described in IBDs [28,194]. Besides their well described roles in metabolic disorders, bile acids have also been shown to play a role in innate immunity, control Treg and Th17 differentiation and regulate wound healing, although beneficial or deleterious effects have been reported depending on the bile acid [195–197]. Thus, dysregulation of bile acid metabolism in IBDs could be part of disease pathogenesis. Accordingly, restoration of intestinal bile acids decreases experimental colitis [197]. Actually, the effects of intestinal microbiota on Treg regulation were dependent on bile acid metabolism [197]. Bile acids, along with SCFAs and the other microbiota-derived metabolites [28], highlight the importance of modulating the gut microbiota in IBD.

9. Sphingolipids

Sphingolipids, such as ceramides, sphingomyelin and sphingosine-1-phosphate (S1P), are a family of molecules that share sphingosine as a common backbone. Sphingolipids are known as structural components of cell membranes but they also have important biological functions and can act as second messengers in the regulation of cell proliferation, migration and survival, as well as in cellular responses to inflammatory stimuli and stress [198,199].

Sphingolipids can be ingested in the diet, endogenously produced or even produced by the intestinal microbiota [200]. Variants of genes involved in sphingolipid metabolism such as ORMDL3 (ORMDL Sphingolipid Biosynthesis Regulator 3) and FADS1 (Fatty Acid Desaturase 1) were associated with IBD [201,202]. In addition, the de novo synthesis of sphingolipids is decreased in colon biopsies from UC patients [203]. Despite the complexity and interconnection of their metabolic pathway (Fig. 3B), interfering with the metabolic enzymes or known receptors of sphingolipids has been more studied than direct administration of these lipids.

The link between abnormal expression of key sphingolipid metabolic enzymes and IBD pathogenesis was extensively investigated in genetically engineered mice models. For example, the expression of SPTLC2, one of the two major subunits of the enzyme serine palmitoyltransferase (SPT) which is involved in the first step of sphingolipid biosynthesis, was found to be decreased in colon biopsies from patients with IBDs [204]. These patients also presented decreased goblet cell number, which was associated with SPTLC2 deficiency as mice harboring intestine-specific Sptlc2-deletion developed features of colitis such as weight loss, diarrhea, rectal bleeding, decreased goblet cell number, and decreased mucin2 production. SPTLC2-deficient mice also had increased circulating lipopolysaccharide levels, which were prevented by the treatment with antibiotics and dexamethasone suggesting that SPT plays a role in maintaining host tolerance to gut bacteria and in gut barrier function [204].

Among sphingolipids, ceramides seem to play a beneficial role in colitis. Depending on the length of the acyl chain, ceramides can be produced by one of six different ceramide synthases (CerS) (Fig. 3B). Mice deficient for CerS2, CerS6 or CerS5 had increased susceptibility to DSS colitis with decreased viability [205–207]. In CerS2-deficient mice, this increased susceptibility was attributed to increased disruption of the epithelial barrier that worsens the ongoing DSS-induced intestinal epithelial damage [206]. CerS6-deficent mice exhibited low colon levels of C16:0-ceramide whereas CerS2-deficient mice exhibited decreased levels of very long chain ceramides (C22 and C24) and increased C16:0-ceramide levels [205,206]. However, inhibition of SPT in CerS2-deficient mice normalized C16:0-ceramide levels and further worsened the intestinal permeability in DSS-induced colitis, which suggests a beneficial role of C16:0-ceramide on epithelial permeability [206]. Contrasting with this suggested effect of C16:0-ceramide, invalidation of CerS5, which produces C14:0-ceramide and C16:0 ceramide, did not affect epithelial permeability [207]. Interestingly, while total CerS5 knockout worsened DSS-induced colitis, mice with colon epithelium-restricted CerS5 invalidation did not show increased susceptibility. Total CerS5 knockout reduced the numbers of CD3+ immune cells, particularly CD8+ T cells, in the colon [207]. Therefore, while CerS2 seems to be implicated in epithelial barrier function, CerS5 seems to be more important for T cell activation and differentiation than epithelial barrier function.

Ceramides can also be the products of sphingomyelin hydrolysis by sphingomyelinases (SMases). Three forms exist for SMases: acidic SMase contributes to lysosomal sphingomyelin turnover, neutral SMase is membrane bound, and alkaline SMase is present in the bile and contributes to the breakdown of dietary sphingolipids. The expression of alkaline SMase was shown to be decreased in UC. Thus, rectal administration of this enzyme protected rats against DSS-induced inflammation [208] suggesting that the hydrolytic products of dietary sphingomyelin have anti-inflammatory effects. This was confirmed in another study where acid SMase inhibition increased mice susceptibility to pathogen-driven colitis [209]. Consistent with these findings, sphingomyelin synthase 2 (SMS2)-deficient mice had increased ceramide levels and were protected from DSS-induced colitis [210].

Besides interfering with their metabolic enzymes, ceramide levels can be altered by administration of sphingomyelin. Orally administered sphingomyelin or feeding with a sphingomyelin-enriched diet exhibited anti-inflammatory properties in experimental models of colitis by modulating the composition of the microbiota and by activating PPARγ [211,212].

Contrasting with these described beneficial effects of ceramides, dietary sphingomyelin-derived ceramides induced the apoptosis of intestinal epithelial cells by increasing cathepsin D, caspase 3 and caspase 9 activity, thus threatening epithelial integrity in a model of DSS-induced colitis in mice [213]. In addition, Sakata et al., showed that the inhibition of acid SMase reduced macrophage activation and C16:0-ceramide levels in vitro, and improved DSS colitis in vivo [214]. Consistent with a deleterious role for ceramides, deficiency of alkaline ceramidase 3, leading to increased levels of C18:1-ceramide, increased lipopolysaccharide-induced expression of pro-inflammatory cytokines in vitro and aggravated DSS-induced colitis in mice [215]. The levels of this ceramide were shown to be increased following activation of murine immune cells or colonic epithelial cells with lipopolysaccharides [215]. C18:1-ceramide also potentiated lipopolysaccharide-induced expression of pro-inflammatory cytokines in these cells [215]. Other in vitro studies also suggest a deleterious role for ceramides in the maintenance of epithelial barrier function [216], possibly due to the presence of ceramides in the membrane and thus alteration of membrane properties when ceramide levels are altered. In fact, ceramides are considered as pro-inflammatory mediators in some settings, such as lung inflammation [217]. In light of these contrasting results, the role of ceramides and their metabolic enzymes remains to be fully understood in the setting of IBD. Indeed, it is not always clear which ceramides are altered when interfering with their metabolic enzymes and whether the levels of other sphingolipids are also altered.

The effects of ceramides in colitis could also be due to ceramide-1-phosphate (C1P) as mice with ceramide kinase deficiency presented more epithelial damage than control littermates [218]. Moreover, C1P levels are expected to increase following the increase of ceramide levels especially that in inflammatory conditions, ceramide kinase can be induced [217,219]. C1P was shown to decrease the production of pro-inflammatory cytokines and chemokines, decrease neutrophil trafficking and increase the production of IL-10 [217,218,220]. C1P also increases the production of prostanoids by enhancing the translocation of $cPLA_2$ to the membrane, its activation and hence the downstream production of PGE_2, that could have beneficial effects in IBDs [217–219,221]. However, depending on the eicosanoids increased and the setting, C1P can also exert pro-inflammatory effects [217]. Actually, different sphingolipids can have opposite effects on $cPLA_2$ expression or activity and thus differently regulate AA metabolism and PG production, which could be part of their effects in IBDs [219].

Besides C1P, it is also important to consider that S1P levels are altered when modulating sphingolipid metabolism and ceramide levels. For instance, S1P levels were increased in the colon of mice deficient for CerS2 and CerS6 [205,206]. Therefore, some of the deleterious effects attributed to decreased ceramide levels in colitis could be due to increased S1P levels. The role of the S1P axis in gastrointestinal diseases [7,222] and the effect of S1P receptor modulators in IBDs [5,223] have been extensively reviewed and are briefly summarized here. S1P binds to several GPCRs ($S1P_{1–5}$), and can activate pro-inflammatory pathways such as the NF-κB pathway and lead to persistent activation of STAT3 [224,225]. The activation of this axis was linked to the sustained inflammation observed in colitis [226,227]. Furthermore, S1P is implicated, mainly through $S1P_1$, in lymphocyte egress from lymphoid tissues and their trafficking to inflammatory sites, an important element in IBD pathogenesis. S1P related genes (synthesis, degradation and signaling) were significantly altered in IBDs [228–230]. Moreover, knockout or pharmacological inhibition of sphingosine kinase, the enzyme that catalyzes the formation of S1P from sphingosine, reduced the severity of murine colitis [228,229]. Actually, this enzyme seems required for TNFα-induced inflammatory responses [228]. Given the pro-inflammatory role of S1P, its implication in lymphocyte trafficking [222,229] and the beneficial effects of selective S1P receptor modulators in pre-clinical models [229,231,232], selective S1P modulators are being tested in clinical trials as a treatment for various autoimmune diseases including CD and UC. S1P receptor modulators are agonists that downregulate S1P receptor expression on lymphocytes and thus their migration. The proposed S1P receptor modulator Amiselimod did not alleviate the symptoms of CD whereas two other S1P receptor modulators, Etrasimod and Ozanimod, successfully delivered histological and endoscopic improvements in phase 2 trials [223]. Phase 3 trials with Ozanimod and Etrasimod in IBD are underway. Besides S1P receptor modulators, monoclonal antibodies against S1P have also been developed with promising results in cancer, but they have not been

investigated in IBD [229].

10. Conclusion

Studying the involvement of lipid mediators in IBDs requires multiple approaches that will allow assessing how the disease affects lipid levels and how the lipid of interest affects the pathophysiology of the disease. Evaluating the consequences of IBDs on lipid levels can be achieved using quantification techniques mainly involving mass spectrometry. While simple in theory, there is quite some variability in the literature (as illustrated in the previous sections) when it comes to determining how CD or UC change the levels of a given lipid. This is in part due to the inherent variability of the diseases, especially for clinical samples and even more so for biopsy sampling. Moreover, the low (and even extremely low) levels of some lipid mediators add methodological issues to the biological variability. Nevertheless, assessing changes in lipid levels, especially if associated with relevant biological markers of the disease, is of great interest. In this work, we reported lipid variations in the colon in experimental models or human biopsies. However, lipid levels have also been assessed in the plasma in an attempt to link lipid levels to disease status and propose biomarkers of disease progression or treatment efficacy.

While the examples discussed in this review clearly support the notion that modulating lipid mediator levels will affect IBDs (Fig. 4), understanding which mechanism(s) mediate(s) their effect remains a complex matter in some cases. As mentioned in Fig. 1, one could modulate bioactive lipid signaling in many ways, by targeting metabolic enzymes or molecular targets. However the use of one or the other strategy depends on the lipids of interest and the interconnectivity of lipid families. Indeed, the direct administration of a lipid mediator is often hampered by its low solubility and its potential enzymatic or chemical degradation. Because the metabolites can be active per se or give rise to active derivatives, it is not an easy task to determine the "active" lipid. When this is the case, administration of agonists or antagonists of the target could be the way to go, as exemplified by S1P receptor modulators. Another useful strategy is the modulation of lipid mediator levels through the inhibition of catabolic or anabolic processes. This is however challenging because of the interconnection of lipid metabolic processes as well as the redundancy of enzymatic processes for most lipid mediators. Inhibition of an enzyme will increase the levels of its substrate but could also decrease the levels of the product lipid, which could have effects in its own right. For instance, inhibition of PLA_2 enzymes has been considered as an anti-inflammatory strategy as it would decrease AA levels and the subsequent production of pro-inflammatory eicosanoids. However, this could also interfere with lysoglycerophospholipid levels. With the same aim to decrease eicosanoid signaling, COX inhibition is another strategy that has proven anti-inflammatory effects, however it is increasingly clear that COX-2 can also play a role in the resolution of inflammation and that several COX-2 metabolites can exert beneficial effects in inflammatory settings [150,233].

Besides inhibiting synthetic enzymes to decrease lipid levels, inhibiting catabolic enzymes is a proven strategy for many lipids. This is the case for instance for endocannabinoids where inhibiting the hydrolytic enzymes is an effective strategy to increase their endogenous levels. This is however not possible for other bioactive lipids such as the SPMs. In this case, the best strategy would be to synthetize agonists of their molecular targets. Moreover, one lipid could be hydrolyzed by several enzymes and when one of these enzymes is inhibited, another could compensate. Additionally, while in vitro biochemical studies can inform of enzyme substrate preferences, the data cannot fully recapitulate the complexity found in vivo.

Thus, for some lipid families, several of the strategies discussed in Fig. 1 could be considered, while for others only a specific strategy could work. Therefore it is crucial to identify lipid mediators, their targets and enzymes, how they are modulated in a given disease and how they affect that disease in order to pinpoint the most effective strategy to interfere with lipid signaling in that particular setting.

It is also essential to use adequate models and pharmacological and molecular tools to study the role of specific lipid mediators, or families of lipid mediators, in IBDs in order to fine tune the therapeutic response.

Although requiring more in-depth studies to fully investigate their roles and implication in IBDs, lipid mediators are clearly involved in IBD pathogenesis as supported by the selected lipid families discussed here. Further unraveling the mechanisms implicated in the effects of lipid mediators in intestinal homeostasis and inflammation should lead to novel therapeutic opportunities.

Highlights

- Bioactive lipids are increasingly studied in inflammatory bowel diseases
- Fatty acids and their metabolites (e.g. prostanoids, SPMs) modulate colon inflammation in IBDs
- Besides S-1-P several lysophospholipids are showing interesting properties in IBDs
- Endocannabinoids are key players of gut physiology having interesting anti-inflammatory properties
- Oxysterols, the bile acids precursors, can control immune cell migration and lymphoid tissue formation in the colon

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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