Emerging roles of metabolites of ω3 and ω6 essential fatty acids in the control of intestinal inflammation

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Abstract

The gastrointestinal tract is continuously exposed to the external environment, which contains numerous non-self antigens, including food materials and commensal micro-organisms. For the maintenance of mucosal homeostasis, the intestinal epithelial layer and mucosal immune system simultaneously provide the first line of defense against pathogens and are tightly regulated to prevent their induction of inflammatory responses to non-pathogenic antigens. Defects in mucosal homeostasis lead to the development of inflammatory and associated intestinal diseases, such as Crohn’s disease, ulcerative colitis, food allergy and colorectal cancer. The recent discovery of novel dietary ω3 and ω6 lipid-derived metabolites—such as resolin, protectin, maresin, 17,18-epoxy-eicosatetraenoic acid and microbe-dependent 10-hydroxy-cis-12-octadecenoic acid—and their potent biologic effects on the regulation of inflammation have initiated a new era of nutritional immunology. In this review, we update our understanding of the role of lipid metabolites in intestinal inflammation.

Keywords: lipid metabolites, dietary oil, intestinal bacteria, inflammatory disease, allergy

Introduction

Worldwide incidences of inflammatory bowel diseases (such as Crohn’s disease and ulcerative colitis), food allergy and colorectal cancer are increasing (1–3). Their pathogenesis is thought to be associated with genetic background, immunological dysfunction, defects in the mucosal or skin barrier, and gut microbiome. In addition, changes in dietary habits and nutrition have been implicated as potential contributors to the increased incidence of intestinal inflammatory diseases. For example, western dietary patterns of high fat intake and limited consumption of fruit and vegetables are associated with increased risk of inflammatory bowel diseases, allergy and colorectal cancer (4–6). In 1978, a cohort study in Greenland Eskimos first revealed the beneficial effect of dietary intake of ω3 fatty acids in preventing cardiovascular disease (7). The balance between ω3 and ω6 fatty acid intakes is recognized as an important factor in the control of allergic and inflammatory diseases in the intestine (8, 9). However, metabolites of ω6 fatty acids are biphasic in inflammation, depending on the types of lipid mediators, receptor usage and target cells. Therefore, in addition to dietary balance between ω3 and ω6 lipids, it is crucial to understand the metabolism of fatty acids in the context of health and diseases.

Conversion of dietary lipids into lipid mediators is an important process to exert bioactivity (9, 10). Accumulating evidence has revealed novel ω3 lipid metabolites, including resolin, protectin, maresin and 17,18-epoxy-eicosatetraenoic acid (17,18-EpETE), as potent pro-resolution or anti-allergy and anti-inflammatory lipid mediators. The recent discovery of these ω3 lipid metabolites and their biologic activity has reignited interest in ω3 lipid research. In addition, we now know that not only mammalian cells metabolize lipids but also intestinal commensal bacteria, which have a unique degradation pathway that yields unique metabolites, including hydroxy fatty acids, oxo fatty acids and conjugated fatty acids. Therefore, the quality of dietary lipids is metabolically associated with the intestinal microbiota for the production of lipid mediators, which may be a critical determinant in the regulation of inflammatory responses. In this review, we discuss current knowledge of the roles of lipid metabolites in the development and control of intestinal inflammation.
ω3 and ω6 essential fatty acids

The terms ω3 and ω6 indicate the chemical structure of various fatty acids, in which a double-bond structure first appears on the third or sixth carbon atoms, respectively, from the methyl end of the fatty acid. Because they lack the specific desaturases that introduce double bonds at these positions, mammalian cells are unable to generate ω3 and ω6 fatty acids; therefore, they are essential fatty acids for humans and must be acquired through the diet. The balance between ω3 and ω6 lipids in the human body thus largely depends on the quality of dietary lipids.

Various types of vegetable oils are commercially available, in which α-linolenic acid and linoleic acid are the major ω3 and ω6 lipids, respectively. After absorption, α-linolenic acid is sequentially metabolized into eicosapentaenoic acid (EPA), n-3 docosapentaenoic acid (n-3 DPA) and docosahexaenoic acid (DHA) through elongation of the carbon chain and the introduction of double-bond structures, whereas linoleic acid is metabolized into arachidonic acid (AA) through these same processes. These fatty acids are further converted into bioactive lipid mediators through the action of cyclooxygenases, lipoxigenases and cytochrome P450 enzymes (CYPs).

ω6 lipid mediators in intestinal inflammation

The linoleic acid that mammals take in from their diets is converted to AA, which is maintained in the phospholipid membrane of cells as a precursor of bioactive eicosanoids. AA-derived prostaglandins (PGs) and leukotrienes (LTs) exert both pro-inflammatory and anti-inflammatory actions in the intestine; these actions are mediated by different types of G protein-coupled receptors (GPRs) (11–13) (Fig. 1). As an example pro-inflammatory role, PGE2, signaling through its receptor EP2 on neutrophils and tumor-associated fibroblasts promotes inflammation in multiple steps to form the tumor microenvironment in colorectal cancer (14). In addition, the PGD2-CRTH2 axis of eicosinotes contributes to the development of dextran sulfate sodium (DSS)- and trinitrobenzene sulfonic acid (TNBS)-induced colitis (15, 16). Indeed, treatment with CRTH2 antagonist inhibits recruitment of eosinophils into the colon (15). Furthermore, LTB4 stimulates its high-affinity receptor BLT1 on dendritic cells (DCs), leading to the production of the pro-inflammatory cytokines IL-6, TNF-α and IL-12, the induction of T17 and T1 cell lines and increased severity of TNBS-induced colitis (17).

In contrast, as examples of the anti-inflammatory roles of AA-derived PGs and LTs, PGE2, signaling through its receptor EP4 has a protective role in DSS-induced colitis by increasing epithelial integrity (18, 19). In addition, the PGD2- DP axis ameliorates DSS-induced colitis and suppresses colorectal cancer (16, 20, 21). As neutrophils isolated from ulcerative colitis patients show a high level of DP expression (16), it is likely that the anti-inflammatory axis of PGD2 targets neutrophils. Indeed, treatment with DP agonist leads to decreased myeloperoxidase activity in the intestine, suggesting that neutrophil migration was inhibited by the PGD2-DP axis (21). Therefore, these findings demonstrate that PGD2 exerts pro- and anti-inflammatory properties through distinct receptor activation; CRTH2-mediated signals induce eosinophil migration while DP-mediated signals inhibit neutrophil migration. These opposing roles of CRTH2 and DP in chemotaxis are explained by different usage of G proteins. Thus, CRTH2 is coupled with Gαi, whereas DP is coupled with Gαq, which induces decreased and increased in cAMP levels, respectively (22). Deficiency of BLT2—a low-affinity receptor for LTB4 but a high-affinity receptor of 12-hydroxyeicosatetraenoic acid (12-HHT)—increases the severity of DSS-induced colitis, suggesting that LTB2- and 12-HHT-mediated BLT2 signaling exerts anti-inflammatory properties (23). Furthermore, in the presence of non-steroidal anti-inflammatory drugs such as aspirin, cyclooxygenases are acetylated; rather than generating PGE2 from AA, acetylated cyclooxygenases produce 15-epi-lipoxin A4, which helps to prevent carcinogenesis (24).

These results demonstrate that ω6 lipid mediators act as both pro- and anti-inflammatory agents (Fig. 1). To delineate their multi-functional roles precisely, future studies likely will focus on characterizing target cells, receptor expression patterns and signaling pathways and on clarifying the metabolic regulation of lipid mediators in the context of health and disease.

ω3 lipid mediators in intestinal inflammation

Because cyclooxygenases, lipoxigenases and CYPs are shared among the substrates of ω6- AA and ω3-EPA, DPA and -DHA, the anti-allergy and anti-inflammatory properties of ω3 fatty acids have long been understood to occur through substrate competition, whereby a high intake of ω3 fatty acids decreases the abundance of AA-derived pro-inflammatory lipid mediators (25) (Fig. 1). Consistent with this understanding, Fat-1 transgenic mice, which carry the ω3 desaturase gene from Caenorhabditis elegans and therefore can synthesize ω3 lipids de novo, show a decreased amount of PGE2 in the colon and decreased pathology during TNBS-induced colitis (26). In addition, Fat-1 transgenic mice are protected against DSS-induced colitis and the development of colorectal cancer (27–29). This animal model supports the notion that an increased ω3/ω6 ratio in the body is beneficial in regard to the regulation of intestinal inflammation through decreased production of ω6-derived pro-inflammatory lipid mediators.

In addition, recent technologic advances in liquid chromatography (LC)- and mass spectrometry (MS)-based analyses of lipid metabolites have enabled the identification of trace metabolites in the body, some of which—the specialized pro-resolving mediators (SPMs) (30–33) (Fig. 1)—have potent pro-resolution activity in inflammation. SPMs include EPA-derived resolvins E1 through E3 (the E-series resolvins), DHA-derived resolvins D1 through D6 (the D-series resolvins), protectin D1, maresins 1 and 2 and maresin conjugates in tissue regeneration 1 through 3 (30–33).

The first study to show that SPMs are involved in the regulation of intestinal inflammation used the TNBS-induced colitis model. Treatment of these mice with resolin E1 increased their survival rate, with sustained body weight and improvement of histologic scores, decreased leukocyte infiltration and decreased the expression of inflammatory cytokines, including IL-12p40, TNF-α and inducible nitric oxide synthase (34). In addition, resolvin E1 was shown to
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The resolvin E1–ChemR23 pathway inhibits TNF-α-induced nuclear translocation of NF-κB and decreases the expression of IL-12p40 and TNF-α by macrophages (35). Furthermore, resolvin E1 activates ChemR23 to induce alkaline phosphatase production and subsequent detoxification of lipopolysaccharide (LPS) in intestinal epithelial cells and promotes CD55-dependent clearance of neutrophils from mucosal surfaces (36, 37). In addition to its effects through the ChemR23-mediated pathway, resolvin E1 serves as a local damper of LTB4–BLT1 signals, as revealed through the use of peritonitis and contact hypersensitivity models (38, 39). Therefore, resolvin E1 targets cells that express ChemR23 or BLT1 (e.g. macrophages, DCs, neutrophils, intestinal epithelial cells) to achieve its pro-resolution effects in inflammation.

After resolvin E1 was discovered, D-series resolvins and maresins were found to exert anti-inflammatory activity in colitis models. For example, in the presence of aspirin, acetylated cyclooxygenases produce 17(R)-hydroxy-DHA, which then undergoes sequential oxygenation by lipoxigenases to result in the production of 17-epi-resolvin Ds, also known as aspirin-triggered resolvin Ds (AT-resolvin Ds) (40). Both resolvin D2 and AT-resolvin D1 prevent the development of DSS- and TNBS-induced colitis in mice (41). In addition, AT-resolvin D1 inhibits inflammatory cytokine production by macrophages in a lipoxin A4 receptor-dependent manner; therefore, blockade of lipoxin A4 receptor reverses the beneficial effects of AT-resolvin D1 in DSS-induced colitis (41). Furthermore, maresin 1, a DHA-derived SPM, has been shown to exert protective activity in DSS- and TNBS-induced colitis (42). Recently, n-3 DPA-derived protectin D1n-3 DPA and resolvin D5n-3 DPA were identified as new SPMs important in intestinal protection (43). These results demonstrate that many types of SPMs have anti-inflammatory effects in colitis models (Fig. 1).

17,18-EpETE as a new class of EPA-derived anti-allergy and anti-inflammatory lipid mediator

Compared with their protective effect in colitis, the role of ω3 lipid mediators in food allergy is less well characterized. Because dietary supplementation with fish oil, which contains high amounts of EPA and DHA, inhibits food allergy (44, 45), ω3 lipid mediators are presumed to be important in the control of allergic responses. In this sense, comprehensive LC-MS/MS-based lipidomic analysis of mice fed an experimental chow that contained linseed oil high in α-linolenic acid or a conventional chow that included soybean oil revealed that 17,18-EpETE acted as an anti-allergy lipid mediator (46). Different formulations of dietary oils have distinct fatty acid compositions, and the soybean oil that is used in conventional mouse chow contains about 50% linoleic acid and
5% α-linolenic acid, whereas linseed oil (also known as flaxseed oil) contains about 60% α-linolenic acid—more than 10 times the amount found in soybean oil. Compared with mice maintained on a control chow containing soybean oil, mice maintained on a diet that included linseed oil had a lower incidence of allergic diarrhea in an ovalbumin-induced food allergy model (46). In addition, imaging MS analysis of the mice revealed that the lipid composition of the colon was correlated with the fatty acid composition of their diet: the colons of mice fed linseed oil contained high levels of α-linolenic acid and its metabolites EPA and DHA, whereas the colons of mice fed soybean oil contained high levels of linoleic acid and its metabolite, AA; these differences were particularly prominent in the lamina propria, where large numbers and various types of immune cells are located, suggesting that the immuno-biologic activity of gut immune cells is influenced by environmental lipid changes (46). Comprehensive LC-MS/MS-based lipidomic analysis revealed that, among the many types of oxygenated lipid metabolites, 17,18-EpETE, a CYP-dependent metabolic product from EPA, was a major product in the colons of the mice fed linseed oil (46). Indeed, injection of synthetic 17,18-EpETE through either a preventive or a therapeutic regimen inhibited the development of allergic diarrhea, suggesting that the anti-allergy effect of dietary linseed oil is mediated—at least in part—by 17,18-EpETE (46).

We recently extended our exploration of the anti-allergy properties of 17,18-EpETE by evaluating its effects on skin allergic inflammation (47). In a hapten-induced contact hypersensitivity model, 17,18-EpETE either preventively or therapeutically ameliorated skin inflammatory signs, including swelling and neutrophil infiltration, in both mice and cynomolgus macaques (47) (Fig. 2). In addition, 17,18-EpETE was effective not only when given intra-peritoneally but also when given orally or topically (47). Because lipid mediators function through the activation of GPRs, we next examined the types of GPRs activated by 17,18-EpETE and found that 17,18-EpETE strongly activated GPR40 (47). Indeed, treatment with GPR40 antagonist or the use of GPR40 knock out (KO) mice erased the anti-inflammatory effects of 17,18-EpETE in skin (47). Consistent with the 17,18-EpETE-induced reduction of neutrophil numbers in inflamed skin, neutrophils expressed the highest levels of GPR40 in the skin (47). In addition, in vitro examination of isolated neutrophils revealed that 17,18-EpETE inhibited neutrophil infiltration by suppressing chemoattractant-induced Rac activation and pseudopod formation in a GPR40-dependent manner (47) (Fig. 2). In contrast to its biologic effects on neutrophils, 17,18-EpETE had little effect on DCs and T cells in the skin—in sharp contrast to the previously revealed anti-inflammatory properties of resolvin E1, which disrupts inducible skin-associated lymphoid tissue during contact hypersensitivity (39, 47). As neutrophils are one of key players in the initiation and development of intestinal inflammation (48, 49), 17,18-EpETE may become new therapeutic agent in the control of intestinal inflammation by regulating neutrophil infiltration in the intestine. In addition, other types of immune cells such as T cells and macrophages take part in the pathogenesis of colitis (50, 51). Therefore, selective use of a single or a mixture of different types of lipid metabolites is a potential strategy for fine-tuning the inflammatory processes in inflammatory diseases.

The enzymatic activity of soluble epoxide hydrolase converts 17,18-EpETE into 17,18-dihydroxy-eicosatetraenoic acid (17,18-diHETE) (52). In models of food allergy and contact hypersensitivity, 17,18-diHETE had little influence on the development of allergic and inflammatory symptoms (46, 47). Consistent with these findings, 17,18-diHETE—unlike 17,18-EpETE—scarcely activated GPR40 (47). Moreover, although GPR40 reportedly recognizes EPA (53), its activation activity was much weaker than that of 17,18-EpETE (47). These findings suggest that the epoxy chemical structure is important for activating GPR40 and exerts anti-allergic and anti-inflammatory properties (Fig. 2). Taken together, these findings...

**Fig. 2.** GPR40-mediated anti-inflammatory properties of 17,18-EpETE. 17,18-EpETE is generated from EPA by CYP. Soluble epoxide hydrolase (sEH) further converts 17,18-EpETE to 17,18-diHETE. 17,18-EpETE is more agonistic for GPR40 than is either EPA or 17,18-diHETE; the potent anti-inflammatory properties of 17,18-EpETE are due to its inhibition of Rac activation and neutrophil migration through GPR40 activation.
indicate that the development of novel strategies for allergic and inflammatory diseases requires both the identification of novel anti-allergic and anti-inflammatory lipid mediators and an improved understanding of the metabolic pathways they regulate.

17,18-EpETE is synthesized from EPA through the enzymatic activity of CYPs. Among CYP subfamilies, CYP1A, CYP2C and CYP2J can convert EPA to 17,18-EpETE (54–56). In addition, a comprehensive analysis of the mouse CYP families involved in the epoxidation of EPA identified five CYP isoforms (mouse Cyp1a2, 2c50, 4a12a, 4a12b and 4f18) with sufficient enzymatic activity to generate 17,18-EpETE from EPA (57). In addition, a reaction's stereochemistry can be important in terms of biologic activity. In this regard, further investigation into the EPA epoxidation reaction driven by each CYP isoform disclosed that Cyp1a2 selectively generated 17(R),18(S)-EpETE, which modulates BK channels in rat cerebral arteries (58), whereas Cyp4f18 yielded 17(S),18(R)-EpETE (57). Cyp4a12a, Cyp4a12b and Cyp2c50 were less stereoselective than Cyp1a2 and Cyp4f18 and thus produced both 17(S),18(R)-EpETE and 17(R),18(S)-EpETE (57). Whether stereoselectivity contributes to the anti-allergy and anti-inflammatory properties of 17,18-EpETE in the regulation of food allergy and contact hypersensitivity is unknown, because previous studies used racemic 17,18-EpETE (46, 47). In addition, CYP genes reportedly contain polymorphisms that can affect the metabolic activity and stereoselectivity of their proteins’ products (59–61). These studies indicate that the expression level of each CYP isoform and its genetic polymorphisms may influence the efficacy of dietary ω3 lipid in controlling inflammatory and allergic diseases.

Microbe-dependent lipid metabolites in the control of intestinal inflammation

Dietary lipid is metabolized by intestinal bacteria, some of which possess unique metabolic pathways that are absent from mammalian cells. For example, intestinal bacteria are able to saturate unsaturated fatty acids (e.g. oleic acid, linoleic acid and α-linolenic acid) to produce hydroxyl fatty acids. In particular, the CLA-HY gene of Lactobacillus plantarum encodes the linoleate 10-hydrolase that converts linoleic acid to 10-hydroxy-cis-12-octadecenoic acid (HYA) (62, 63) (Fig. 3). HYA is further metabolized to 10-oxo-cis-12-octadecenoic acid (KetoA) and 10-oxo-trans-11-octadecenoic acid (KetoC) by the bacterial enzymes CLA-DH and CLA-DC, respectively (62, 64) (Fig. 3), and KetoC is metabolized to either 10-hydroxy-trans-11-octadecenoic acid (HYC) by CLA-DH or 10-oxo-octadecanoic acid (KetoB) by CLA-ER (62) (Fig. 3). HYC acts as a direct substrate of conjugated linoleic acids (CLAs), including cis-9,trans-11-CLA and trans-9,trans-11-CLA, whereas CLA-DH and CLA-HY metabolize KetoB to 10-hydroxy-octadecanoic acid (HYB) and oleic acid, respectively (62) (Fig. 3). These metabolic pathways are considered to be a detoxifying mechanism of anaerobic rumen bacteria (65, 66).

Interestingly, some of the bacterial metabolic products just described are biologically active modulators of the host organism’s health and disease. For example, HYA feeding increases the expression of claudin 1, subsequently enhancing tight junctions between skin cells and thus inhibiting atopic dermatitis (67). Moreover, treatment with HYA protects mice from periodontitis by suppressing bacteria-induced degradation of E-cadherin in the gingival tissue (68). KetoA plays a role in preventing obesity by activating transient receptor potential vanilloid 1 and enhancing noradrenaline turnover in adipose tissue (69). Furthermore, KetoA promotes adipocyte differentiation by activating peroxisome proliferator-activated receptor γ (70) and by inhibiting liver X receptor α, thus decreasing the production of triacyl glycerol (71). In its anti-inflammatory role, KetoC activates macrophage GPR120 and decreases the LPS-mediated induction of the inflammatory cytokines TNFα and IL-6 (72). Therefore, these linoleic acid-derived, bacteria-dependent metabolites play important roles in the control of host health. HYA reportedly ameliorates DSS-induced colitis by down-regulating TNFR2 expression and thus suppressing inflammation-induced epithelial barrier defects in intestinal epithelial cells (73). These findings suggest that the use of intestinal bacteria to promote HYA production, or probiotic treatment with HYA-producing bacteria, is a potential therapeutic strategy in the control of intestinal inflammatory diseases (Fig. 4).

Bacteria that produce HYA from linoleic acid include L. plantarum (74), L. acidophillus (75), Enterococcus faecalis (76), Streptococcus bovis (76), Strep. pyogenes (77), Stenotrophomonas maltophilia (79). In addition to CLA-HY in L. plantarum, enzymes that generate HYA from linoleic acid include

![Fig. 3. Unique lipid metabolism by Lactobacillus plantarum. Lactobacillus plantarum has metabolic pathways for the saturation of unsaturated fatty acids by unique enzymes; this process is absent in mammals. Some of the bacterial metabolic intermediates help control inflammation in the host mammal.](image-url)
FA-HY2 in *L. acidophilus* (80), SPH in *Strep. pyogenes* (77) and OhyA1-2 in *Steno. maltophilia* (79); all of these were annotated previously as myosin-cross-reactive antigen (MCRA) proteins (Fig. 4). Because MCRA family proteins are widely conserved among bacteria, many microbial species likely produce HYA from linoleic acid (81). Therefore, investigating the efficiency of HYA production among these organisms is one potential way to select the most effective probiotics. Another possible strategy for controlling the amount of HYA in the body is to modulate the metabolic pathway of linoleic acid→HYA→KetoA. For example, dietary intake of bacteria that have CLA-HY or MCRA but lack CLA-DH may be a means to enhance HYA levels.

Compared with the intense investigation into the biological activity of linoleic acid-derived microbial metabolites such as HYA, little information is available on α-linolenic acid-derived microbial metabolites. In general, enzymes that are involved in linoleic acid metabolism also convert α-linolenic acid into its respective 10-hydroxy products (62). Future studies will reveal the influences of dietary ω3 lipid in the context of microbe-dependent metabolites in the control of intestinal inflammation.

**Conclusion**

Lipid mediators play key roles in the regulation of intestinal inflammatory diseases. In addition to the recent progress in the characterization of host-dependent novel lipid metabolites (e.g. resolvin, protectin, maresin, 17,18-EpETE) as anti-inflammatory and anti-allergy mediators, the discovery of the potent bioactivity of microbe-dependent metabolites, including HYA, reveals a functional relationship among dietary lipid quality, the intestinal microbiome and the host immune system in the regulation of mucosal homeostasis and development of inflammatory diseases. Therefore, omics technologies, including metabolome analysis and intestinal flora analysis, are poised to become powerful tools in increasing our understanding of the gastrointestinal environmental system in intestinal immunity.

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**Fig. 4.** Beneficial effect of HYA in protecting the intestinal epithelial barrier and thus preventing the development of colitis. HYA is generated by linoleate-10-hydration activity owing to enzymes such as CLA-HY, FA-HY2, SPH, OhyA1, OhyA2 and MCRA in several types of bacteria. HYA in turn down-regulates the expression of TNFR2 in intestinal epithelial cells and thus exerts a protective function against TNF-mediated barrier impairment.
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