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Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis

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Abstract

Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid, display a wide range of beneficial effects in humans and animals. Many of the biological functions of PUFAs are mediated via bioactive metabolites produced by fatty acid oxygenases such as cyclooxygenases, lipoxygenases and cytochrome P450 monooxygenases. Liquid chromatography–tandem mass spectrometry-based mediator lipidomics revealed a series of novel bioactive lipid mediators derived from omega-3 PUFAs. Here, we describe recent advances on omega-3 PUFA-derived mediators, mainly focusing on their enzymatic oxygenation pathway, and their biological functions in controlling inflammation and tissue homeostasis.

Keywords: anti-inflammation, LC–MS/MS, lipid mediator, omega-3 fatty acid, oxygenase

Introduction

Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), display a wide variety of effects favorable for a healthier life. A large number of epidemiological studies and clinical trials suggest a beneficial relationship between omega-3 PUFA consumption and reduced inflammatory symptoms (1). Furthermore, genetic evidence obtained by *fat-1* (a *Caenorhabditis elegans* gene encoding omega-3 fatty acid desaturase) transgenic mice revealed that a higher omega-3 to omega-6 PUFA ratio in tissues confers anti-inflammatory and/or tissue-protective phenotypes (2).

Many of the biological actions of PUFAs are mediated via bioactive lipid mediators produced by fatty acid oxygenases such as cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 monooxygenases (CYPs) (3, 4). For example, omega-6 arachidonic acid (AA) is released from membrane phospholipids in response to inflammatory stimuli, and subsequently converted into eicosanoids such as prostaglandins (PGs), leukotrienes (LTs) and lipoxins (LXs) in a COX- and LOX-dependent manner (Fig. 1). Omega-3 PUFAs such as EPA, DPA and DHA are also available at sites of inflammation for enzymatic conversion to bioactive mediators. The anti-inflammatory effect of omega-3 PUFAs is thought to occur not only by competing with the formation of eicosanoids from AA, but also by providing alternative metabolites with less potent activity than that of AA-derived mediators (5–7). Recent advances in liquid chromatography–tandem mass spectrometry (LC–MS/MS)-based lipidomics uncovered a novel series of lipid mediators derived from omega-3 PUFAs (8, 9). Emerging evidence suggests that uncontrolled inflammation may contribute to a progression to chronic inflammatory states, including cardiovascular diseases, autoimmune diseases, fibrosis and cancer (10, 11). Understanding the molecular mechanisms of how elevated omega-3 PUFA levels control inflammation and tissue homeostasis will lead to a new class of therapeutic applications. In this review, we describe recent advances in the understanding of how omega-3 PUFAs are metabolized into bioactive mediators, as well as their functional roles in controlling inflammation and tissue homeostasis.

Bioactive mediators derived from omega-3 PUFAs: specialized pro-resolving mediators

In response to tissue injury or microbial infection, polymorphonuclear leukocytes (PMNs) are recruited to the site of injury. Locally accumulated PMNs execute phagocytosis of bacteria and/or cellular debris to clear the site of injury. Consequently, monocyte-derived macrophages are recruited to the injured site to carry out efferocytosis (phagocytosis of apoptotic PMNs and cellular debris) and to therefore promote the resolution of acute inflammation (3). Resolution of inflammation

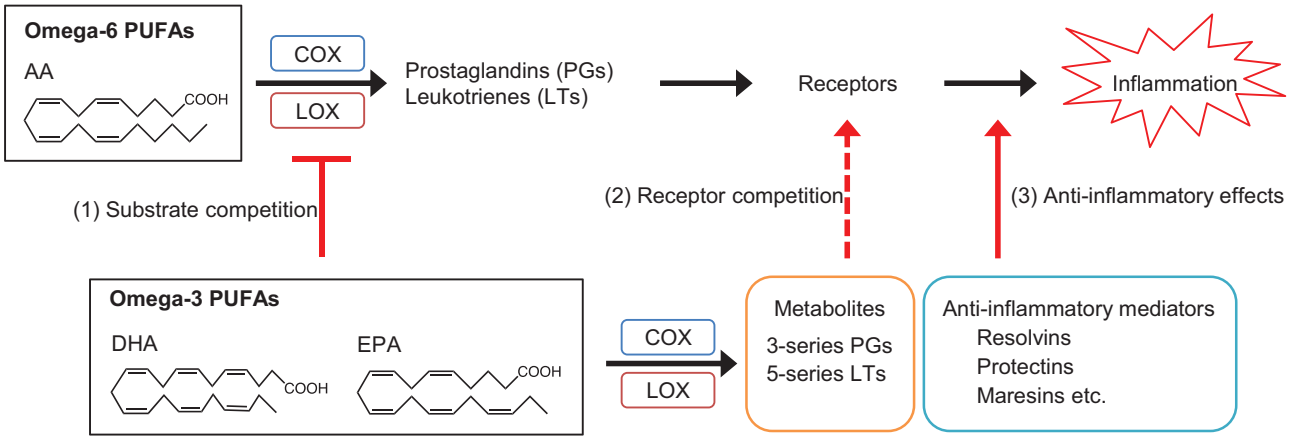


Fig. 1. Anti-inflammatory effects of omega-3 PUFAs. Omega-3 PUFAs exert their beneficial effects by the following mechanisms: (1) substrate competition with omega-6 AA, (2) receptor competition and (3) conversion into anti-inflammatory metabolites.

is an active, well-orchestrated process governed by specific cell types and soluble mediators, including PUFA-derived lipid mediators (3, 8, 12).

By using LC–MS/MS-based lipidomics, a series of specific pro-resolving mediators (SPMs) derived from omega-3 PUFAs were identified (8, 9). They included EPA-derived resolvins (E-series resolvins: RvE1–E3; Fig. 2), DHA-derived resolvins (D-series resolvins: RvD1–D6; Fig. 3), protectins (PD1 and PDX; Fig. 3) and maresins (MaR1 and MaR2; Fig. 3). Moreover, sulfide conjugates for tissue regeneration, namely resolvin conjugates in tissue regeneration (RCTR1, RCTR2 and RCTR3), protectin conjugates in tissue regeneration (PCTR1, PCTR2 and PCTR3) and maresin conjugates in tissue regeneration (MCTR1, MCTR2 and MCTR3), were identified (Fig. 3). Biosynthesis of MCTRs begins with 14-lipoxygenation of DHA to yield 13,14-epoxy-maresin, and subsequent enzymatic insertion of glutathione at the C-13 position by LT C4 synthase or glutathione S-transferase mu 4 to form MCTR1 (13, 14). MCTR1 is then converted to MCTR2 by the second enzyme, γ-glutamyl transferase, to remove a γ-glutamyl group from MCTR1, followed by conversion to MCTR3 by the third enzyme, dipeptidase, that cleaves a cysteinyl–glycinyl bond of MCTR2 (14, 15). In contrast, RCTR and PCTR are generated via 17-lipoxygenation of DHA and may undergo further enzymatic conversion in a similar way as in the case of precursor formation of RvDs (7,8-epoxy-17-hydroxy-DHA) and PDs (16,17-epoxy-protectin) (16). Then, they are processed to conjugate with glutathione to yield RCTRs and PCTRs (16, 17). Also, DPA-derived SPMs were referred to as $RvD1_{n\text{-}3\ DPA}$, $RvD2_{n\text{-}3\ DPA}$, $RvD5_{n\text{-}3\ DPA}$, $PD1_{n\text{-}3\ DPA}$, $PD2_{n\text{-}3\ DPA}$, $MaR1_{n\text{-}3\ DPA}$, $MaR2_{n\text{-}3\ DPA}$, $MaR3_{n\text{-}3\ DPA}$ and 13-series resolvins (RvT1–T4; Fig. 4).

Their biological actions are mediated through various types of cells such as PMNs, macrophages, dendritic cells, eosinophils, innate lymphoid cells, $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells and B cells (8, 9, 18). Of note, several sulfide conjugates have unique bioactivity of promoting tissue regeneration in planaria possibly through extracellular signal-regulated kinase-mediated regulation of gene expression pathways (13), in addition to inhibiting PMN infiltration, stimulating phagocytosis of bacteria and efferocytosis of apoptotic cells in leukocytes (Fig. 3). The *in vivo* activity of omega-3 PUFA-derived mediators in controlling inflammation and its resolution has been best characterized in murine acute inflammation models (8, 12, 19). In zymosan-induced sterile peritonitis, RvE1 and PD1 promoted the resolution of inflammation by limiting excessive PMN infiltration, activating macrophage efferocytosis and enhancing the egress into draining lymph nodes of leukocytes containing engulfed zymosan (12, 19–21). In addition, RvD1 and RvD5 significantly reduced the number of bacteria in blood and peritoneal exudate in *Escherichia coli*-inoculated mice, possibly through macrophage phagocytosis-stimulating activity (22).

Furthermore, SPMs also impact on several disease models such as colitis (23), sepsis (24, 25), lung injury (26), myocardial infarction (27), liver ischemia–reperfusion injury (28), cancer (29), allergic dermatitis (30), psoriasis (18) and experimental autoimmune disorders (31). In the skin disease models, RvE1 attenuated dendritic cell activation, which may inhibit an accumulation of $CD4^+$ or $CD8^+$ T cells in the draining lymph node as well as of IL-17-producing γδ T cells in the inflamed skin (18, 30). Moreover, in experimental autoimmune encephalitis, RvD1 suppressed autoreactive T-cell immune responses by decreasing polarization to T_h1 and T_h17 while increasing T_{reg} (31). Notably, a recent *in vitro* study demonstrated that RvD1, RvD2 and MaR1 not only attenuated T_h1 and T_h17 polarization, but also enhanced T_{reg} generation in human $CD4^+$ T cells (32). This evidence supports the notion that SPMs serve a wide range of beneficial effects in not only acute inflammation associated with innate immune responses, but also chronic inflammation associated with adaptive immune responses (Figs 2–4). Furthermore, several unique functions of SPMs have been described, including autophagy and inflammasome regulation, indicating their pleiotropic roles in regulating inflammation and maintaining tissue homeostasis (Fig. 3) (33, 34).

Omega-3 oxygenation pathways: a cause of beneficial effects of omega-3 PUFAs?

In the E-series resolvins biosynthetic pathway, EPA is initially converted to 18-hydroxy-eicosapentaenoic acid (18-HEPE),

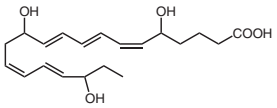
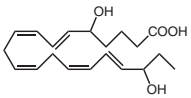
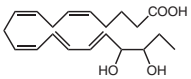
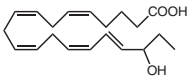
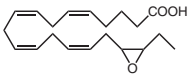
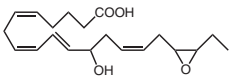
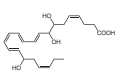
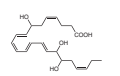
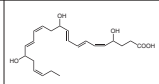
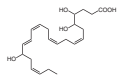
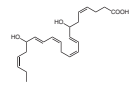
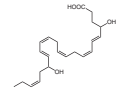
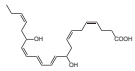
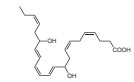
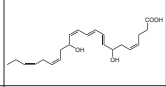
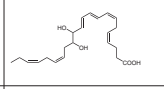
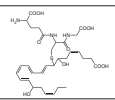
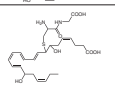
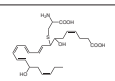
Name	Structure	Function
RvE1		·Inhibits PMN infiltration (20, 68) ·Enhances phagocytosis-induced PMN apoptosis (69) ·Promotes macrophage efferocytosis (20, 70) ·Reduces pro-inflammatory cytokines (71) ·Improves dermatits models (18, 30)
RvE2		·Inhibits PMN infiltration (72, 73) ·Promotes macrophage phagocytosis (72)
RvE3		·Reduces PMN infiltration (36, 74) ·Inhibits PMN chemotaxis (36, 74) ·Prevents preterm birth (75)
18-HEPE		·Attenuates fibroblast activation (37) ·Inhibits cardiac remodeling (37) ·Restores mitochondorial dysfunctions (38) ·Inhibits metastasis (39) ·Reduces adhesion of monocytes to endothelial cells (40)
17,18-EpETE		·Inhibits degranulation of mast cells (43) ·Reduces adhesion of monocytes to endothelial cells (40) ·Inhibits neutrophil migration (44) ·Activates PPAR-γ in bronchi (52) ·Modulates TRPV4 activity (54) ·Reduces inflammatory cytokines (59)
12-OH-17,18-EpETE		·Inhibits PMN infiltration (60) ·Attenuates PMN chemotaxis and polarization (60) ·Reduces ovalbmin-induced inflammatory cell accumulation (61)

Fig. 2. Structures and functions of EPA-derived bioactive metabolites.

an omega-3 oxygenated product of EPA, followed by oxygenation via 5-LOX and/or 12/15-LOX present in leukocytes (Fig. 5) (35, 36). In addition to being a precursor for E-series resolvins, 18-HEPE also confers cardioprotective effects in pressure overload-induced maladaptive remodeling and heart failure (transverse aortic constriction model) (37). 18-HEPE is locally produced by bone marrow-derived macrophages recruited to heart tissue in response to pressure overload, thereby inhibiting the local activation of fibroblasts and the development of cardiac remodeling (37). Also, 18-HEPE restored mitochondrial dysfunction, including the decrease in respiration and membrane potential frequently observed during inflammation (38). In a cancer model, 18-HEPE inhibited metastasis of B16-F0 melanoma cells through a decrease in C-X-C motif chemokine receptor 4 expression (39). In addition, 18-HEPE reduced tumor necrosis factor-α-induced endothelial activation and monocyte adhesion by attenuating activation of the nuclear factor-κB pathway (40). DHA-derived 20-hydroxy DHA (20-HDoHE), an omega-3 oxygenated product of DHA, was also generated *in vivo*, and further metabolized to 14,20-dihydroxy DHA (14,20-diHDoHE) that blocked PMN infiltration in mouse zymosan-induced acute peritonitis (41).

EPA is also converted to epoxy-containing metabolites such as 17,18-epoxyeicosatetraenoic acid (17,18-EpETE). In general, 17,18-EpETE displays biological activities, while its corresponding diol, namely 17,18-dihydroxyeicosatetraenoic acid (17,18-diHETE), has less activity. DHA is also metabolized to 19,20-epoxydocosapentaenoic acid (19,20-EpDPE) with various bioactivities and is further converted to the corresponding diol (42). A dietary intake of omega-3 PUFA-enriched food represented highly elevated EPA-derived mediators, including 17,18-EpETE (43). The administration of 17,18-EpETE, but not of 17,18-diHETE, displayed protective activity in a murine gut allergic diarrhea model through inhibition of the degranulation of mast cells, as well as in a dinitrofluorobenzene-induced dermatitis model via blockade of neutrophil mobility (43, 44).

Soluble epoxide hydrolase (sEH), expressed in many tissues, is a cytosolic enzyme with epoxide hydrolase activity (45). The administration of an sEH inhibitor or deletion of the *sEH* gene displayed several beneficial effects in various murine inflammatory disorders, including diet-induced hepatitis (46, 47) as well as lipopolysaccharide- or bleomycin-induced lung injury (48, 49), along with the significant

Name	Structure	Function
RvD1		•Inhibits PMN infiltration (3, 12) •Promotes macrophage efferocytosis (3, 12) •Improves experimental autoimmune model (31) •Activates macrophage autophagy (33) •Reduces inflammatory cytokines (76) •Stimulates polarization of macrophage from M1 to M2 (77) •Inhibits Th1 and Th17 polarization, enhances Treg generation (32) •Blocks class switching of naive B cells to IgE-secreting B cells (78)
RvD2		•Inhibits PMN infiltration (3, 12) •Promotes macrophage efferocytosis (3, 12) •Enhances nitric oxide production in endothelial cells (3) •Improves survival rate in sepsis (25) •Inhibits activation of inflammasome in macrophages (34) •Reduces inflammatory cytokines (76) •Inhibits Th1 and Th17 polarization, enhances Treg generation (32)
RvD3		•Inhibits PMN infiltration (79) •Reduces inflammatory cytokines (79) •Restores barrier function of epithelial cells (79) •Attenuates inflammation in peritonitis and arthritis (79)
RvD4		•Reduces PMN infiltration (80) •Promotes macrophage phagocytosis and efferocytosis (80) •Enhances fibroblast efferocytosis (80) •Protects from peritonitis and skin inflammation (80)
RvD5		•Stimulates PMN phagocytosis (22) •Protects against *E. coli* infection (22)
RvD6		•Produced during coagulation process in the presence of adenosine deaminase (81)
PD1		•Inhibits PMN infiltration (20, 21) •Promotes macrophage efferocytosis (3, 20) •Regulates T cell migration (3, 21) •Increases C-C chemokine receptor type 5 expression on PMNs (82) •Inhibits production of inflammatory cytokines (83) •Reduces expression of CD11b and CD62L on eosinophils (84)
PDX		•Decreases inflammation of dextran sulfate sodium (DSS) colitis (23) •Inhibits platelet aggregation (85) •Inhibits PMN activation (86)
MaR1		•Inhibits PMN infiltration (3, 21) •Promotes macrophage efferocytosis (21) •Reduces inflammatory cytokines (76) •Inhibits Th1 and Th17 polarization, enhances Treg generation (32) •Stimulates production of amphiregulin in innate lymphoid cells (87)
MaR2		•Inhibits PMN infiltration (88) •Promotes macrophage efferocytosis (88)
RCTR1		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (16, 17) •Promotes tissue regeneration in planaria (16, 17) •Limits PMN chemotaxis (17)
RCTR2		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (16, 17) •Promotes tissue regeneration in planaria (16, 17) •Limits PMN chemotaxis (17)
RCTR3		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (17) •Promotes tissue regeneration in planaria (17) •Limits PMN chemotaxis (17)

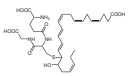
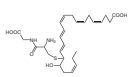
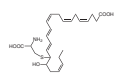
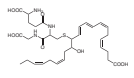
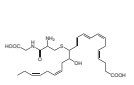
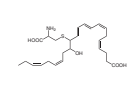
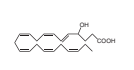
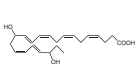
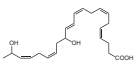
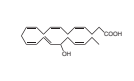
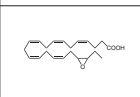
Name	Structure	Function
PCTR1		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (16, 89) •Promotes tissue regeneration in planaria (16, 89) •Reduces inflammatory cytokines (89) •Limits PMN chemotaxis (89)
PCTR2		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (16) •Promotes tissue regeneration in planaria (16)
PCTR3		•Stimulates macrophage phagocytosis of bacteria and efferocytosis of apoptotic PMNs (16)
MCTR1		•Promotes tissue regeneration in planaria (13, 15) •Stimulates leukocyte phagocytosis of bacteria and macrophage efferocytosis of apoptotic PMNs (13, 15)
MCTR2		•Promotes tissue regeneration in planaria (13, 15) •Stimulates leukocyte phagocytosis of bacteria and macrophage efferocytosis of apoptotic PMNs (13, 15)
MCTR3		•Promotes tissue regeneration in planaria (15) •Stimulates leukocyte phagocytosis of bacteria and macrophage efferocytosis of apoptotic PMNs (15)
4-HDoHE		•Activates PPAR-γ (90)
14,20-diHDoHE		•Inhibits PMN infiltration (41)
14,21-diHDoHE		•Enhances wound healing (91) •Promotes production of VEGF and IL-10 in macrophages (92) •Reduces hyperglycemia-induced ROS generation in macrophages (92)
17-HDoHE		•Promotes antibody-mediated immune response (93) •Promotes macrophage phagocytosis (94) •Reduces inflammation in DSS-induced colitis (94) •Reduces obesity-associated inflammation (95) •Prevents hyperalgesia with adjuvant-induced arthritis (96)
19,20-EpDPE		•Limits palmitate-induced lipid droplet accumulation (50) •Inhibits tumor growth and metastasis (51) •Surpresses VEGF-induced angiogenesis (53)

Fig. 3. Structures and functions of DHA-derived bioactive metabolites.

increases in fatty acid epoxides, such as 17,18-EpETE and 19,20-EpDPE, through the inhibition of corresponding diol formation (50). Co-treatment of adipocytes with 17,18-EpETE or 19,20-EpDPE and an sEH inhibitor blocked palmitate-induced lipid droplet accumulation *in vitro* (50). This effect of omega-3 epoxides was suggested to occur through the regulation of autophagy and the endoplasmic reticulum stress response, which may contribute to prevent high-fat diet-induced obesity (50). Moreover, exogenously administered 19,20-EpDPE suppressed vascular endothelial growth factor (VEGF)-induced angiogenesis, as well as tumor growth and metastasis in the presence of an sEH inhibitor (51).

Emerging evidence has yielded potential target molecules for 17,18-EpETE. For example, 17,18-EpETE-activated G protein-coupled receptor (GPR) 40 results in the inhibition of GTP-bounded Rac formation and subsequent neutrophil migration *in vitro* (44). In addition, 17,18-EpETE activates peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor, in human bronchi (52). The administration of 17,18-EpETE or 19,20-EpDPE also alleviated symptoms in an

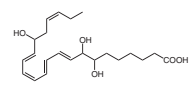
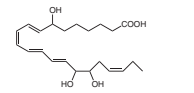
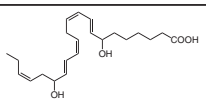
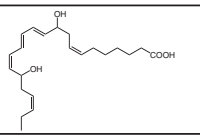
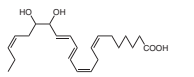
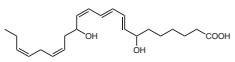
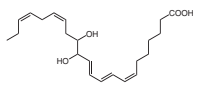
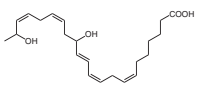
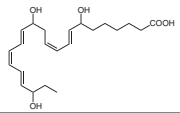
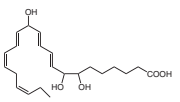
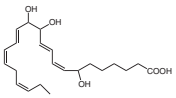
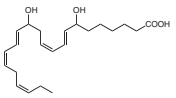
Name	Structure	Function
$RvD1_{n\text{-}3\ DPA}$		▪Reduces cytokine levels (97) ▪Inhibits PMN chemotaxis and adhesion to endothelial cells (97) ▪Enhances macrophage phagocytosis (97)
$RvD2_{n\text{-}3\ DPA}$		
$RvD5_{n\text{-}3\ DPA}$		▪Ameliorates DSS-induced colitis (98) ▪Inhibits neutrophil-endothelial cell adhesion (98)
$PD1_{n\text{-}3\ DPA}$		
$PD2_{n\text{-}3\ DPA}$		▪Reduces adhesion molecule expression (simultaneously treatment with $PD1_{n\text{-}3\ DPA}$) (97)
$MaR1_{n\text{-}3\ DPA}$		▪Reduces cytokine levels (97) ▪Inhibits PMN chemotaxis and adhesion to endothelial cells (97) ▪Enhances macrophage phagocytosis (97)
$MaR2_{n\text{-}3\ DPA}$		
$MaR3_{n\text{-}3\ DPA}$		▪Produced in the peritoneal exudate (97)
RvT1		▪Improves mouse survival during bacterial infection (99) ▪Enhances macrophage phagocytosis of bacteria, production of reactive oxygen species, and efferocytosis of apoptotic PMNs (99) ▪Reduces activation of the inflammasome (99)
RvT2		
RvT3		
RvT4		

Fig. 4. Structures and functions of DPA-derived bioactive metabolites.

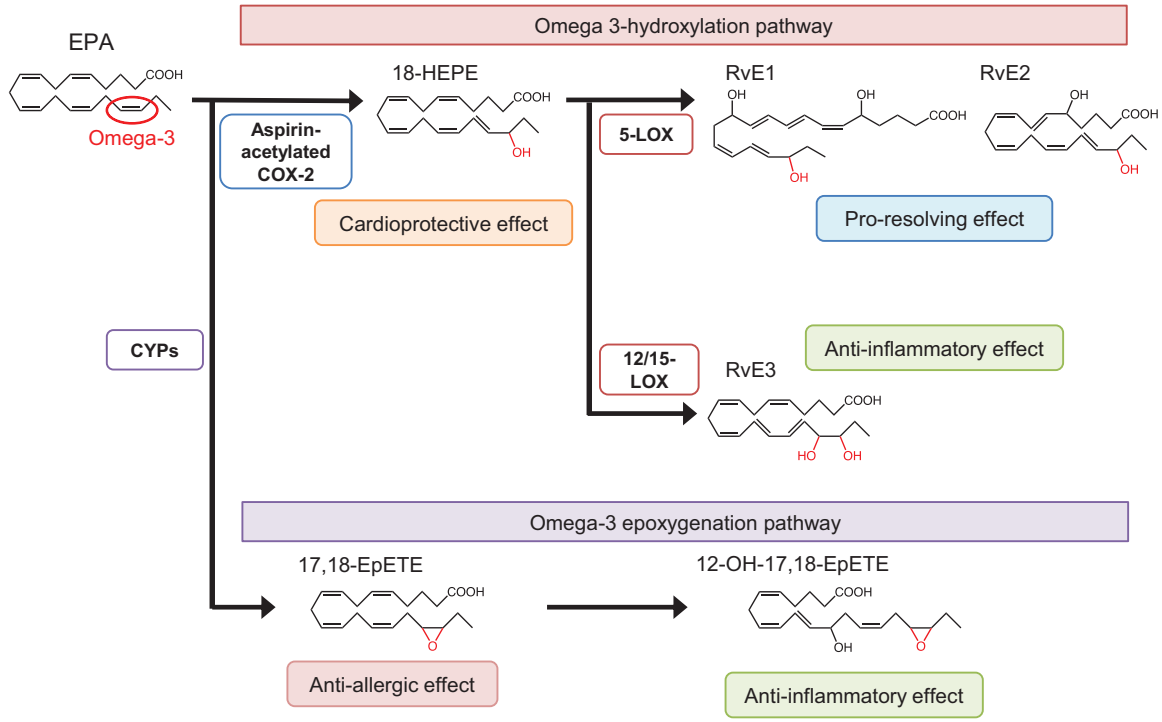


Fig. 5. EPA metabolome through the omega-3 oxygenation pathway. 18-HEPE, a common precursor of E-series resolvins, is generated by aspirin-acetylated COX-2 from EPA. RvE1 and RvE2 are produced via 5-LOX, and RvE3 is generated via 12/15-LOX. Epoxygenation of omega-3 double bond is catalyzed by several CYP enzymes to produce 17,18-EpETE, and its secondary product 12-OH-17,18-EpETE which also has anti-inflammatory activity.

age-related macular degeneration model, possibly through a PPAR-γ-dependent mechanism (53). 17,18-EpETE incorporated with plasma membrane phospholipids may modulate the activity of the transient receptor potential (TRP) V4 channel, a polymodal ion channel involved in vasodilation, by changing the mechanical properties of the membrane environment (54). GPR40, PPAR-γ and TRPV4 are expressed in various immune cells, suggesting their contribution in regulating various inflammatory responses (44, 55–58).

Moreover, studies on the structure-specific role of omega-3 epoxides or its derivatives revealed that 17,18-EpETE, but no other regioisomers (8,9-, 11,12-, 14,15-EpETE), inhibited the palmitate-induced expression of pro-inflammatory cytokines in peritoneal macrophages, presumably through the inhibition of c-Jun N-terminal kinase phosphorylation (59). Studies on the structure-specific role of omega-3 epoxide also demonstrated that 12-hydroxy-17,18-epoxyeicosatetraenoic acid (12-OH-17,18-EpETE), one of the mono-oxygenated metabolites of 17,18-EpETE, is formed *in vivo* and displayed anti-inflammatory activity (Fig. 5) (60). The chemotaxis of neutrophils was inhibited *in vitro* by 12-OH-17,18-EpETE, while 17,18-EpETE and 12-HETE did not possess this activity (60). The two natural isomers of 12-OH-17,18-EpETE, namely 12*S*-OH-17*R*,18*S*-EpETE and 12*S*-OH-17*S*,18*R*-EpETE, were active, while unnatural stereoisomers (12*R*-isomers) were inactive (60). Similarly, 12-OH-17,18-EpETE, but not 17,18-EpETE, decreased ovalbumin-induced inflammatory cell accumulation in bronchoalveolar lavage fluid in an airway inflammation model (61).

Hydroxylation of omega-3 carbon of EPA is reported to be catalyzed by aspirin-acetylated COX-2 or microbial CYP enzyme to produce 18*R*-HEPE (Fig. 5) (35). Epoxygenation of the olefin double bond of PUFAs is mainly mediated by CYPs to yield fatty acid epoxides (Fig. 5) (42). A comprehensive analysis of mouse *CYP* genes was recently conducted, and five isoforms, namely Cyp1a2, 2c50, 4a12a, 4a12b and 4f18, were identified to confer omega-3 epoxidation of EPA to yield 17,18-EpETE (62). DHA was also effectively converted into 19,20-EpDPE by these enzymes. Of interest, Cyp1a2 and Cyp4f18 displayed high stereoselectivity with quite opposite geometry to form 17*R*,18*S*-EpETE and 17*S*,18*R*-EpETE, respectively. It is reported that 17*R*,18*S*-, but not 17*S*,18*R*-EpETE, had the potential to activate calcium-activated potassium (BK) channels expressed in vascular smooth muscle cells to exert a vasorelaxation effect (63). These results suggest that the omega-3 oxygenation pathway may hold a key for the beneficial effects of omega-3 PUFAs by structure-specific mechanisms in controlling inflammation and tissue homeostasis.

Conclusions

Uncontrolled inflammation leads to a chronic inflammatory state, resulting in the progression of refractory disease, including autoimmune diseases, obesity, fibrosis and cancer (3, 10, 11). The precise determination of the molecular mechanisms that control inflammation and the resolution process will aid in the development of a new class of anti-inflammatory therapies. Omega-3 PUFA-derived specialized pro-resolving mediators such as resolvins, protectins and maresins are potential candidates to be developed as new therapeutics (64,

65). Also oxygenation at the site of the omega-3 double bond that distinguishes omega-3 PUFAs from other fatty acids may play an important role for the beneficial effects of dietary omega-3 PUFAs in keeping human health and tissue homeostasis (4). Therefore, enhancement of this metabolic pathway may have therapeutic implications in controlling inflammation and related diseases. For example, the use of sEH inhibitor and/or stable analogs that enhance the half life of omega-3 PUFA epoxides *in vivo* and may be therapeutically useful (50, 66, 67). Further studies of the biosynthesis, metabolism and target molecules (receptors) at the molecular levels would help us to understand their physiological importance in maintaining tissue homeostasis, and also as potential therapeutic targets for inflammation and related diseases.

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