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Review

Lipoxygenase Pathways in the Regulation of Vascular Inflammation and Its Resolution

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Abstract: Inflammation is associated with vascular diseases, including atherosclerosis. The inflammatory response in the blood vessel involves cellular interactions between endothelial cells and monocytes/macrophages, and inflammatory mediators. Lipoxygenase (LOX) enzymes play an important role in inflammatory responses through the formation of lipid mediators. The 5-LOX pathway, primarily active in leukocytes such as monocytes/macrophages, converts arachidonic acid (AA) to leukotrienes (LTs), which are pro-inflammatory mediators that contribute to various vascular pathologies. In contrast, LOX pathways also generate specialized pro-resolving lipid mediators (SPMs), highlighting a dual role in both the initiation and resolution of inflammation. SPMs, formed by 5-LOX, 12-LOX and 15-LOX enzymes, are polyunsaturated fatty acid (PUFA)-derived anti-inflammatory and inflammation-resolving mediators that have important functions in the resolution of inflammatory processes. Dysregulation of the balance between pro-inflammatory leukotrienes and SPMs contributes to chronic vascular inflammation and disease progression. These mediators have been implicated in the treatment of vascular diseases with therapeutic strategies including LT receptor antagonists, 5-LOX-activating protein (FLAP) inhibitors, and approaches aimed at enhancing SPM pathways showing potential. This review provides an overview of the regulation of vascular inflammation and resolution by LOX pathways, and presents recent evidence on the role of LOX-derived lipid mediators in vascular inflammation and its resolution.

Keywords: Lipoxygenase; vascular inflammation; leukotrienes; specialized pro-resolving lipid mediators; resolution of inflammation

1. Introduction

Vascular Inflammation and Its Resolution

Inflammation is a physiologic response to various stimuli such as infections and tissue injury. The inflammatory response in blood vessels involves activation of the endothelium, which results in recruitment of leukocytes and production of inflammatory mediators [1]. 5-LOX is mainly expressed in leukocytes and converts AA into LTs [2]. LTs are pro-inflammatory mediators that increase vascular permeability and the recruitment of leukocytes to the inflammatory site, and play an important role in inflammatory diseases [3]. Inflammation contributes to a number of vascular pathologies such as atherosclerosis and thrombosis [4]. Termination of the inflammatory response, 'resolution', is an active process involving different mediators [5]. The mediators that participate in the resolution

process are SPMs including lipoxins, resolvins, protectins and maresins. These lipid mediators are formed from PUFAs such as omega-6 fatty acid AA, or omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by the action of LOX enzymes [6]. SPMs exhibit anti-inflammatory effects and promote the resolution of inflammation by decreasing leukocyte recruitment and inducing phagocytosis of apoptotic cells by macrophages, a process called 'efferocytosis' [7]. Dysregulation of the resolution process leads to chronic inflammation, which is associated with cardiovascular diseases [8].

Cardiovascular diseases remain the leading cause of death worldwide despite advances in therapeutic strategies [8]. Current treatments including lipid-lowering agents and antiplatelet drugs have significantly reduced acute cardiovascular events. However, these approaches do not primarily modulate the underlying inflammatory processes that drive cardiovascular disease progression. As a result, a large proportion of patients continue to exhibit residual inflammatory risk, highlighting the need for novel therapeutic approaches [9,10].

Inflammation is increasingly recognized as a driver of cardiovascular diseases [8]. While inflammatory response is essential for host defense, chronic inflammation in blood vessel is associated with vascular pathologies. Emerging evidence indicates that failure of resolution contributes to the development of vascular diseases such as atherosclerosis [8]. Lipid mediators, generated by LOX pathways, play an important role in the regulation of vascular inflammatory responses. Through formation of LTs, 5-LOX regulates vascular processes such as endothelial permeability and leukocyte adhesion. Research on 5-LOX pathway has focused primarily on the roles of LTs in asthma and allergic diseases. However, accumulating data now implicate LTs in vascular diseases such as atherosclerosis and aortic aneurysm [4,11]. Also, 12-LOX and 15-LOX pathways have shown to be involved in vascular pathologies such as atherosclerosis [12,13], and 12-LOX- and 15-LOX-derived eicosanoids are implicated in thrombosis and coronary artery disease (CAD) [13,14]. Consequently, targeting LOX pathways offer a new approach to cardiovascular disease treatment. SPMs, generated by 5-LOX, 12-LOX and 15-LOX pathways, have emerged as regulators of the resolution process. These mediators, through their inflammation resolving effects, represent a new strategy for the treatment of cardiovascular diseases. This review summarizes the roles of LOX pathways in the regulation of vascular inflammation and resolution, and discusses LOX-based treatment approaches in cardiovascular diseases. In this review, we aim to provide an overview of LOX pathways in vascular inflammation and its resolution, with a focus on the balance between pro- and anti-inflammatory lipid mediators in cardiovascular diseases.

2. Methods of Review

Relevant literature was identified through searches of PubMed. Key terms related to 'LOX Pathways in the Regulation of Vascular Inflammation and Resolution' were used. Priority was given to recent, high-quality studies and influential publications. Articles were selected based on relevance to the topic.

3. Lipoxygenase Pathways in Vascular Inflammation

3.1. Different Roles of 5-LOX, 12-LOX and 15-LOX

LOX are enzymes that catalyze the oxygenation of PUFAs such as AA. 5-LOX is present in leukocytes (neutrophils, basophils, eosinophils, and monocyte/macrophages) and other immune cells such as mast cells and dendritic cells [2]. Expression of 5-LOX is induced by pro-inflammatory stimuli or during cell differentiation by transforming growth factor-β (TGF-β) and vitamin D3 in monocytes [2,15]. The 5-LOX pathway generates LTs, which are pro-inflammatory lipid mediators that play a role in several diseases [3,16,17]. 5-LOX can also regulate the generation of specific microRNAs (miRNA) involved in immune responses and cell proliferation [2]. Upon an inflammatory stimulus, AA is converted to 5S-hydroperoxyeicosatetraenoic acid (5S-HPETE) by 5-LOX, in association with FLAP. 5S-HPETE is further converted by 5-LOX to the unstable intermediate leukotriene A_4 (LTA_4) [18]. In resting cells 5-LOX is a soluble enzyme. Upon cell activation, 5-LOX translocates to the nuclear membrane where it interacts with FLAP for catalysis (Figure 1). Translocation of 5-LOX from the cytoplasm to the nucleus was observed in monocytes during cell differentiation [3]. AA is liberated from membrane phospholipids by the action of cytosolic phospholipase A_2 ($cPLA_2$) (Figure 1). Leukocyte stimulation leads to translocation of both 5-LOX and $cPLA_2$ to the nuclear membrane [3]. FLAP transfers the substrate AA to 5-LOX, which converts AA to LTA_4 (Figure 1). The synthesis of 5-LOX products in the cell is a tightly regulated process, and interaction with FLAP influences 5-LOX product formation [19]. LTA_4 is either converted to the dihidroxy LTB_4 by LTA_4 hydrolase (LTA_4H), or conjugated with gluthathione to form LTC_4 by LTC_4 synthase (LTC_4S) [20] (Figure 1). Subsequent peptide cleavage of the gluthathione moiety forms LTD_4 and LTE_4, and these three products (LTC_4, D_4, E_4) are called cysteinyl leukotrienes (cysLTs). LTs exert their effects through G protein-coupled receptors (GPCR), BLT1 and BLT2 for LTB_4, and cysLT1 and cysLT2 for LTC_4 and D_4 have been identified

(Figure 1). LTB_4 is a chemoattractant for leukocytes, while LTC_4 and D_4 are potent bronchoconstrictors, increase microvascular permeability and mucus secretion, and are involved in the pathogenesis of asthma [3]. CysLT1 has a high-affinity to LTD_4, and is targeted by antiasthma drugs such as montelukast. LTs also play a role in cardiovascular diseases. LTB_4 contributes to monocyte-endothelial adhesion and has been implicated in atherosclerosis [4]. CysLTs increase endothelial permeability, potentiate platelet activation, cause vascular smooth muscle cell (VSMC) contraction [21], and play a role in aortic aneurysms [11].

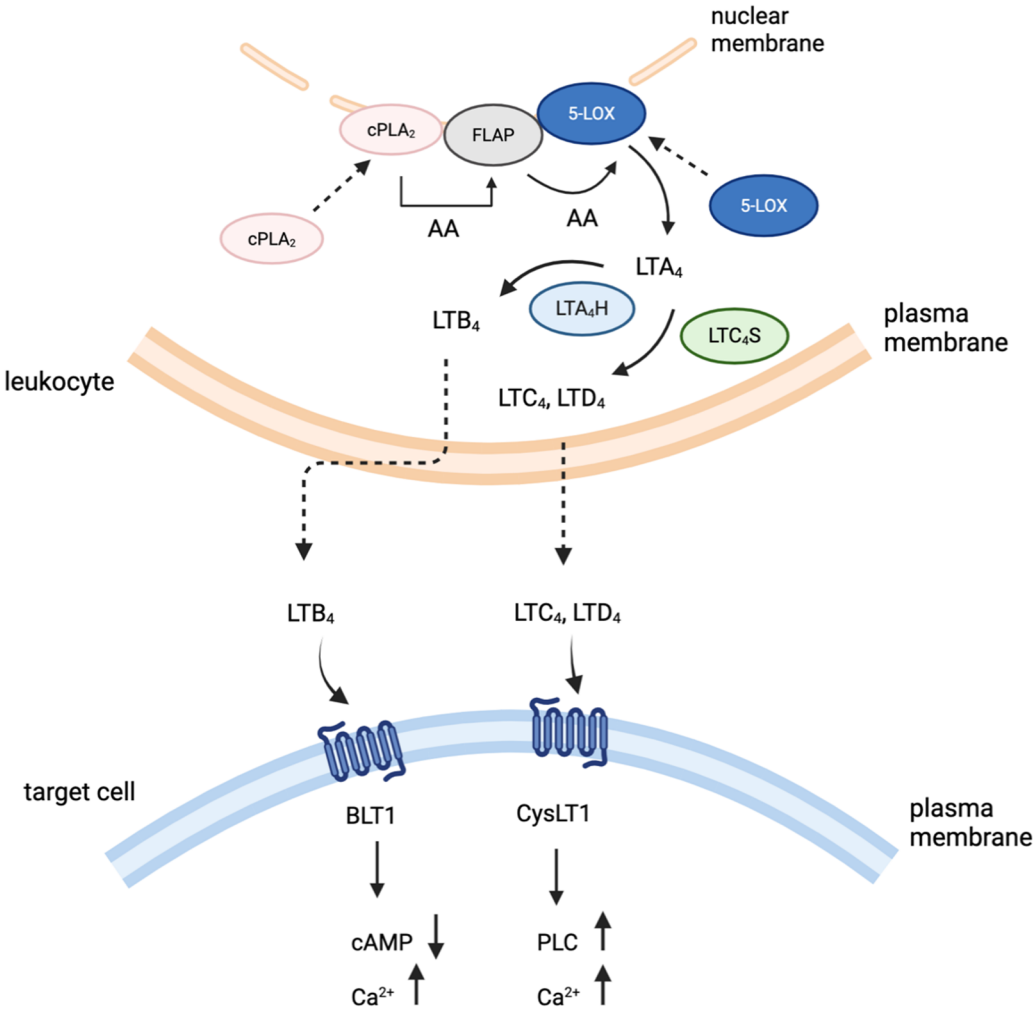

Figure 1. Cellular biosynthesis and signaling of LTs. 5-LOX is expressed in leukocytes. Upon stimulation, 5-LOX and $cPLA_2$ translocate from the cytoplasm to the nuclear membrane. AA is released from membrane phospholipids by the action of $cPLA_2$. FLAP transfers AA to 5-LOX, which converts AA to LTA_4. LTA_4 can be further converted to LTB_4 by LTA_4H or to LTC_4 and LTD_4 by LTC_4S. LTB_4 exhibit its effects on target cells through their receptor BLT1, and LTC_4 and D_4 through CysLT1 receptor. Activation of BLT1 and CysLT1 by LTs leads to increased intracellular Ca^{2+}. $cPLA_2$ cytosolic phospholipase A_2, AA arachidonic acid, FLAP 5-LOX-activating protein, 5-LOX 5-lipoxygenase, LTA_4 leukotriene A_4, LTA_4H LTA_4 hydrolase, LTC_4S LTC_4 synthase, cAMP cyclic AMP, PLC phospholipase C, Ca^{2+} calcium.

LOX enzymes are also involved in the formation of SPMs, which are lipid mediators that have anti-inflammatory and inflammation resolving (pro-resolving) effects (Figure 2) [6]. These mediators have important functions in the resolution of inflammatory responses, including limitation of leukocyte infiltration, counter-regulation of pro-inflammatory mediators, promotion of M2 (resolutive) macrophage phenotype and increased efferocytosis [22]. SPMs exert their biological actions through their GPCR receptors [23]. During an inflammatory response, a lipid mediator class switch occurs, which results in a shift from the production of pro- to anti- inflammatory mediators by LOX enzymes [24,25]. 5-LOX can produce SPMs by using AA, 15-hydroxyeicosatetraenoic acid (15-HETE), 18-hydroxyeicosapentaenoic acid (18-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHA) as substrates [6]. 12-LOX forms SPMs by using AA and DHA as substrates for the formation of SPMs, while 15-LOX uses AA, DHA and 18-HEPE as substrates [6].

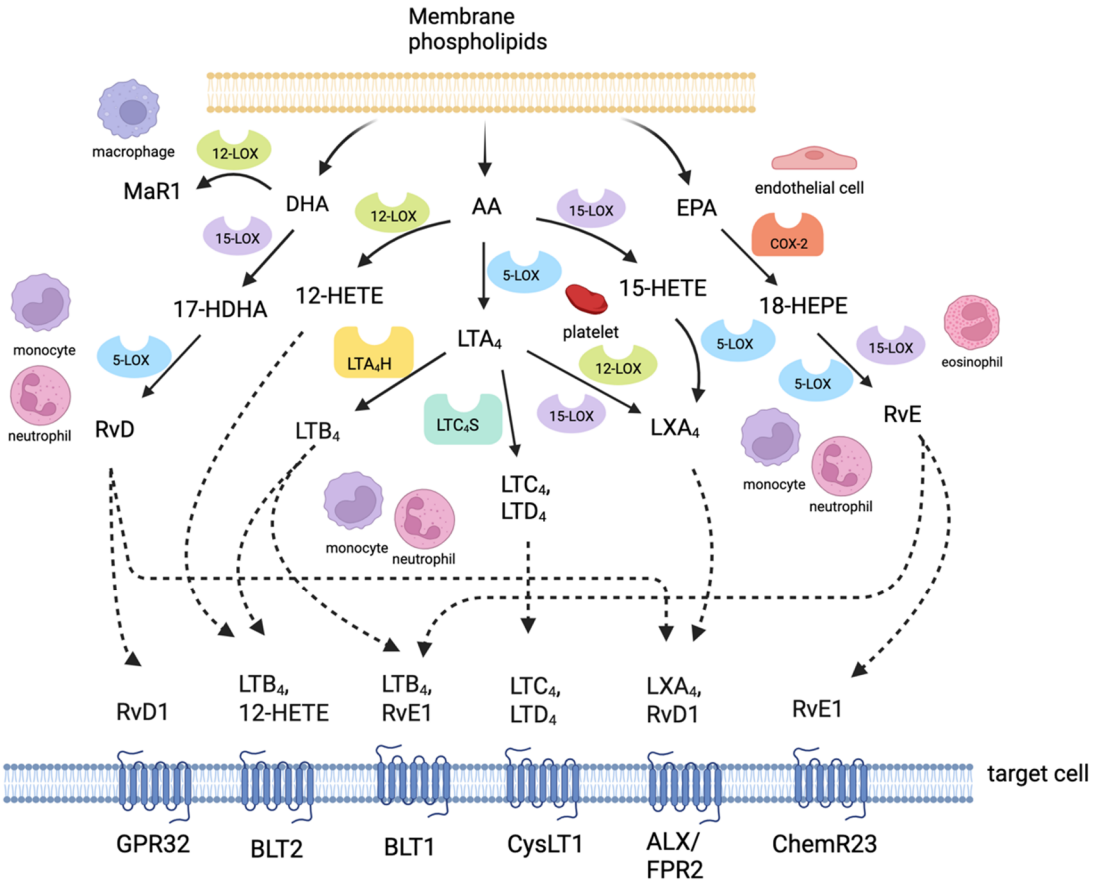

Figure 2. Biosynthesis pathways and receptors of PUFA-derived eicosanoids. 5-LOX converts AA to LTA_4, which is further converted to LTB_4 by LTA_4H or to cysLTs (LTC_4, LTD_4) by LTC_4S. LTB_4 binds to BLT1 or BLT2, and cysLTs (LTC_4 and LTD_4) bind to CysLT1. 12-HETE can also bind to BLT2. LXs can be generated via transcelluar biosynthesis involving 5-LOX and 12-LOX or 15-LOX. AA can be converted to 12-HETE by 12-LOX and to 15-HETE by 15-LOX. 15-HETE can be further converted to LXs by 5-LOX. RvEs are generated from EPA by COX-2 and 5-LOX or 15-LOX. RvDs are formed from DHA by 15-LOX and 5-LOX. DHA can be converted to MaR1 by 12-LOX. SPMs (LXA_4, RvE1, RvD1) bind to their respective receptors (ALX/FPR2, ChemR23, GPR32) on target cells. RvE1 and RvD1 can also bind to BLT1 and ALX/FPR2, respectively. Cell types involved in the biosynthesis pathways are indicated: neutrophils (5-LOX), monocytes (5-LOX, 15-LOX), eosinophils (15-LOX), macrophages (12-LOX), platelets (12-LOX), and endothelial cells (COX-2). AA arachidonic acid, 5-LOX 5-lipoxygenase, LTA_4 leukotriene A_4, LTA_4H LTA_4 hydrolase, LTC_4S LTC_4 synthase, 12-HETE 12-hydroxyeicosatetraenoic acid, LXA_4 lipoxin A_4, EPA eicosapentaenoic acid, COX-2 cyclooxygenase-2, 18-HEPE 18-hydroxyeicosapentaenoic acid, RvE1 resolvin E1, DHA docosahexaenoic acid, 17-HDHA 17-hydroxydocosahexaenoic acid, RvD1 resolvin D1, MaR1 maresin 1, ALX/FPR2 formyl peptide receptor 2, ChemR23 chemokine-like receptor 1.

Lipoxin A_4 (LXA_4) and LXB_4 are generated by the actions of 5-LOX and 12-LOX or 15-LOX enzymes through transcellular biosynthesis [6]. Platelets express 12-LOX, which can take up and convert leukocyte-derived LTA_4 to LXA_4 and LXB_4 [6]. Alternatively, lipoxins can be generated by the action of the antiplatelet drug aspirin, via aspirin-acetylated cyclooxygenase-2 (COX-2), which gives rise to aspirin-triggered lipoxins (ATL) [26]. This suggests that aspirin may have additional beneficial effects in the management of cardiovascular diseases. 15-LOX is present in eosinophils, monocyte-macrophages, reticulocytes and airway epithelial cells and its expression is induced during differentiation of monocytes to M2-like macrophages [24]. Uptake of apoptotic cells via activation of lipoxin receptors upregulates 15-LOX expression in macrophages [25]. LXA_4 and LXB_4 can also be synthesized by the sequential action of 15-LOX and 5-LOX [6], with recent studies indicating that M2 polarization of macrophages leads to a lipid mediator class switch from 5-LOX to 15-LOX pathway [24,27].

LOX enzymes can also generate SPMs from the omega-3 fatty acids EPA and DHA (Figure 2). 5-LOX is involved in the formation of resolvins from EPA and DHA [6], which are classified as EPA-derived E-series resolvins (RvE) and DHA-derived D-series resolvins (RvD). Resolvins can be formed by the sequential action of 15-LOX and 5-LOX [6]. Lipoxin and resolvin synthesis by the LOX pathways involves the action of FLAP [28],

while SPM formation from DHA occurs independently of FLAP [19]. The first identified E-series resolvin, RvE1, counter-regulates leukocyte activity, reduces platelet aggregation and thromboxane A_2 (TXA_2) formation, and initiates resolution of inflammation through repolarization of macrophages toward resolution-type macrophages [29]. A new member of E-series resolvins, RvE4, stimulates human macrophage efferocytosis *in vitro* [7]. RvD5 increases phagocytosis in macrophages [30]. DHA can be converted by 15-LOX to protectins (PD), and by 12-LOX to maresins (MaR) in leukocytes [31]. MaR1 stimulates efferocytosis and has homeostatic functions on platelets [32].

Also, 12-LOX and 15-LOX can form eicosanoids that have pro-inflammatory effects in the blood vessels (Figure 2). 12S-HETE, which is formed by the action of 12-LOX from AA, potentiates platelet activation and thrombin generation, is a vasoconstrictor, and increases monocyte-endothelial adhesion [33–35]. 15S-HETE, 15-LOX product of AA, has a pro-aggregatory effect on platelet function [14], and increases clot formation [36]. 15-LOX has also been implicated in atherogenesis by promoting the oxidation of low-density lipoprotein (LDL) and increasing foam cell formation [12]. These findings show that 5-LOX mainly drives pro-inflammatory leukotriene production, whereas 12-LOX and 15-LOX pathways can have both pro-inflammatory and pro-resolving roles depending on the cellular context. Table 1 summarizes the expression, substrates, products and biological functions of 5-LOX, 12-LOX and 15-LOX enzymes.

Table 1. Expression, substrates, products and biological functions of LOX enzymes involved in vascular diseases.

Enzyme	Expression	Substrates	Products	Biological Functions Associated with Vascular Diseases
5-LOX	Neutrophils, monocytes, macrophages, eosinophils, mast cells, dendritic cells	AA, 15-HETE, 18-HEPE, 17-HDHA	LTB_4, LTC_4, LTD_4, LTE_4 LX, RvE, RvD	Monocyte-endothelial adhesion, endothelial permeability platelet activation, vasoconstriction Inhibition of platelet aggregation, inhibition of leukocyte infiltration, stimulation of macrophage efferocytosis
12-LOX	Platelets, macrophages, epithelial cells	AA, DHA	12-HETE MaR1	Platelet activation, thrombin generation, vasoconstriction, monocyte-endothelial adhesion Stimulation of macrophage efferocytosis, homeostatic functions in platelets
15-LOX	Monocytes, macrophages, eosinophils, epithelial cells	AA, DHA, 18-HEPE	15-HETE RvE, RvD, PD	Platelet aggregation, clot formation, oxidation of LDL, foam cell formation Inhibition of leukocyte infiltration, stimulation of macrophage efferocytosis

BLT1 receptor is predominantly found in leukocytes, while BLT2 is expressed in a variety of cells including endothelial cells [37]. 12S-HETE can also bind to BLT2, a low-affinity receptor for LTB_4 [33]. Activation of BLT1 by LTB_4 leads to inhibition of cyclic AMP (cAMP) synthesis and increased intracellular calcium (Ca^{2+}), which in turn increases leukocyte chemotaxis. LTB_4 activation of BLT1 and BLT2 in monocytes leads to the activation of nuclear factor-kappa B (NF-κB) [37]. CysLT1 and CysLT2 activation leads to increased intracellular Ca^{2+} RvE1 binds to the chemokine-like receptor 1 (ChemR23), which is expressed in monocyte/macrophages, platelets and VSMC [29]. MaR1 was shown to suppresses NF-κB activation in endothelial cells *in vitro* [38]. These mechanisms affect both intracellular signaling and interactions between cells in the vascular wall especially between monocytes/macrophages and endothelial cells.

3.2. Monocyte/Macrophage—Endothelial Cell Interactions

Endothelial communication plays key role in the inflammatory response in blood vessels. Endothelial cells comprise the vascular endothelium, which has various functions including regulation of vascular tone and permeability, maintenance of homeostasis and coagulation, and coordination of the inflammatory response [39]. The vascular endothelium functions as an important gatekeeper, which regulates the movement of inflammatory cells including monocytes/macrophages. Monocytes are circulating leukocytes, which interact with endothelial cells to participate in the inflammatory response. As an inflammatory response develops, various cytokines and inflammatory mediators act upon the blood vessels and induce increased expression of endothelial cell-adhesion molecules, activating the endothelium [1]. Chemokines such as interleukin-8 (IL-8), IL-6 and monocyte chemoattractant protein-1 (MCP-1) released by endothelial cells, cause monocytes to move to the inflammatory site by inducing the adherence of these cells to the vascular endothelium [1] (Figure 3A,B). Monocytes differentiate to macrophages upon inflammatory stimuli, releasing inflammatory cytokines such as IL-1β, IL-6 and tumor

necrosis factor-α (TNF-α) [24] (Figure 3A,B). These cytokines increase vascular permeability. Both TNF-α and IL-1β induce increased expression of adhesion molecules on vascular endothelial cells [1] (Figure 3A). IL-1β and TNF-α also act on macrophages and endothelial cells to induce production of the chemokines that contribute to the influx of leukocytes by increasing their adhesion to endothelial cells (Figure 3A). In addition, TNF-α activates macrophages, promoting increased phagocytic activity [1].

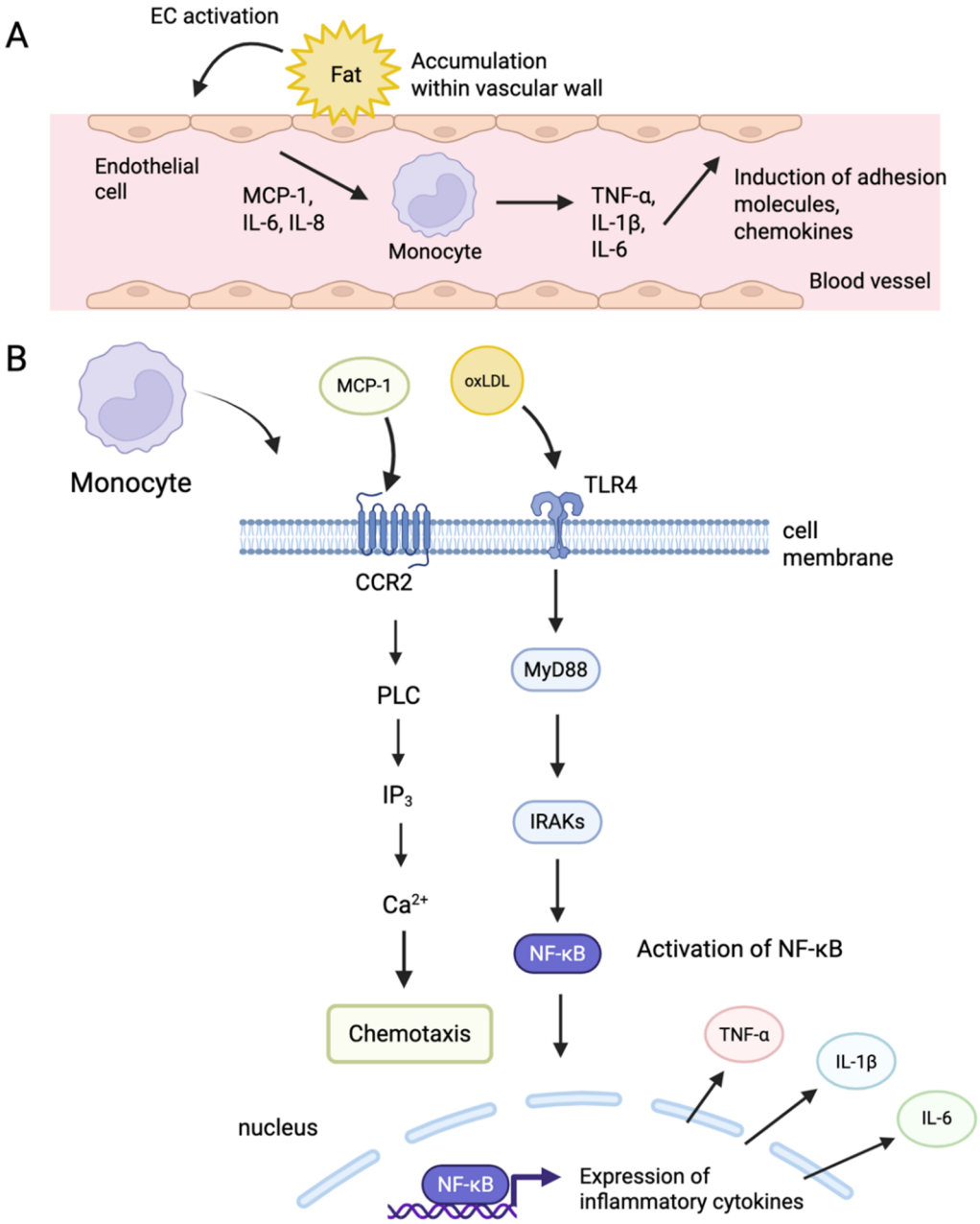

Figure 3. Monocyte-endothelial cell interactions in vascular inflammation. (**A**) Atherosclerosis involves lipid accumulation within vascular wall, which activates endothelial cells. Activated endothelial cells release chemokines (MCP-1, IL-6, IL-8) to recruit monocytes. Monocytes release inflammatory cytokines (TNF-α, IL-1β, IL-6) that act back on endothelial cells to induce increased expression of adhesion molecules and chemokines, thereby promoting further monocyte recruitment, and propagating vascular inflammation. (**B**) Upon inflammatory stimulus, endothelial cells release chemokines such as MCP-1 that bind to CCR2 receptors on monocytes and induce chemotaxis. OxLDL can bind to TLR4 receptors on monocytes, leading to NF-κB activation, which induces the production of inflammatory cytokines (TNF-α, IL-1β, IL-6). EC endothelial cell, MCP-1 monocyte chemoattractant protein-1, IL-6 interleukin-6, TNF-α tumor necrosis factor-α, oxLDL oxidized low-density lipoprotein, CCR2 C-C chemokine receptor type 2, TLR4 Toll-like receptor 4, MyD88 myeloid differentiation primary response 88, IRAK interleukin-1 receptor-associated kinase, NF-κB nuclear factor-kappa B, PLC phospholipase C, IP_3 inositol trisphosphate, Ca^{2+} calcium.

5-LOX is mainly expressed in leukocytes such as monocytes/macrophages, and induced upon inflammatory stimuli [2]. LTs, generated by the 5-LOX pathway, increase endothelial cell permeability and monocyte-endothelial adhesion [2]. SPMs, generated through cellular interactions via LOX pathways upon lipid mediator class switching [6,24], attenuate the expression of adhesion molecules, decrease the release of pro-inflammatory cytokines, and counter-regulate leukocyte-endothelial interactions [39]. M2 polarization in macrophages is associated with a decrease in prostaglandin E_2 (PGE_2) formation [6]. 15-LOX expression is induced during differentiation of monocytes to M2-like macrophages by IL-4 or IL-13 [24]. M2 polarization of macrophages is suggested to lead to a lipid mediator class switch from 5-LOX to 15-LOX pathway [24,27]. SPMs reduce expression of endothelial cell adhesion molecules, which in turn reduces monocyte adhesion and infiltration to the inflammatory site, promoting the transition toward resolution phase. RvE1 induces polarization of macrophages toward resolution-type macrophages [29]. RvE1 also activates the BLT1 receptor in leukocytes, inhibiting the pro-inflammatory actions of LTB_4 [29]. Aspirin-triggered lipoxin A_4 (AT-LXA_4) directly increases plasma nitric oxide (NO) levels and inhibits leukocyte–endothelial interactions [26]. RvE4 and RvD5 were shown to enhance macrophage phagocytosis and efferocytosis, which is an important function of SPMs for tissue repair [7,30]. MaR1 inhibits TNF-α induced monocyte adhesion in endothelial cells [38]. In a chronic inflammatory response, large numbers of activated macrophages release reactive oxygen species (ROS) that cause tissue damage, and are implicated in vascular pathologies involving oxidative stress such as endothelial dysfunction and atherosclerosis. LXA_4, RvE1 and RvD1 were shown to reduce TNF-α induced ROS generation in endothelial cells [39].

Vascular inflammation is an important driver of cardiovascular diseases [40–43], such as atherosclerosis (Figure 3A), which can lead to thrombosis and myocardial infarction [4,44]. Atherosclerosis involves foam cells, which are macrophages transformed by the endocytosis of oxidized low-density lipoprotein (oxLDL) [45]. Accumulation of foam cells can result in occlusion of coronary arteries and rupture of atheromatous plaques. LTB_4 was shown to contribute to the pathogenesis of atherosclerosis [4]. The imbalance between pro- and anti-inflammatory mediators was found to be associated with atherosclerotic plaque stability, and the RvD1/LTB_4 ratio was reported to be decreased in human vulnerable atherosclerotic plaques [8]. Dysregulation of the balance between pro-inflammatory leukotrienes and SPMs, often associated with impaired efferocytosis, defective SPM biosynthesis, and persistent activation of inflammatory signaling pathways such as NF-κB (Figure 3B), contributes to chronic vascular inflammation and disease progression. Impairment of efferocytosis is suggested to play an important role in the shift towards inflammation in the vascular wall and plaque instability [46]. In atherosclerosis, proteolytic cleavage of the efferocytosis receptor MER proto-oncogene tyrosine kinase (MERTK) reduces the ability of plaque macrophages to clear dead cells in atherosclerotic lesions, which contributes to plaque necrosis and impaired resolution [46]. LOX-derived eicosanoids have also shown to be involved in the impairment of efferocytosis. 12(S)-HETE suppressess apoptotic cell internalization by activating Ras homolog family member A (Rho A) in atherosclerosis [13].

Macrophage-derived 15-LOX contributes to LDL oxidation and foam cell formation, and increases atherosclerosis progression [12]. 12-LOX is involved in vascular inflammation in atherosclerosis, and excessive activation of 12-LOX in early atherosclerosis was found to be associated with impairment of AMP-activated protein kinase (AMPK)-dependent regulation of vascular metabolism [47]. SPMs promote plaque stability and make them less prone to rupture by inducing a switch of macrophage phenotypes to M2-like macrophages and by decreasing inflammatory cytokines [8,48]. RvE1 has atheroprotective effects through activation of its receptor ChemR23 in macrophages such as decreased oxLDL uptake and increased phagocytosis [49]. RvD2 reduces atherosclerosis, necrotic core area, and enhances macrophage phagocytosis in hyperlipidemic mice via GPR18 signaling [50]. RvD2 limits necrosis in atherosclerotic plaques by decreasing senescent macrophages [48]. Also, lipoxins were shown to inhibit foam cell formation [51] and have atheroprotective effects by modulating leukocyte function in atherosclerosis [52]. In an advanced lesion, VSMC proliferate and progressively constrict the artery. When the endothelium becomes injured, thrombocytes and coagulation factors are activated and initiate blood clotting, causing acute thrombus formation. MaR1 regulates platelet functions by inhibiting the release of pro-inflammatory and pro-thrombotic mediators [32]. RvD4 reduced thrombus formation in an animal model of deep vein thrombosis [53]. Also, inhibition of 12/15-LOX was shown to be protective against cerebral ischemia by reducing microvessel constriction and microthrombi formation after subarachnoid hemorrhage in mice [54].

5-LOX was shown to promote VSMC pyroptosis, an inflammatory programmed cell death, through NF-κB pathway, thereby promoting AAA formation in mice [55]. MaR1 inhibited VSMC activation, increased macrophage efferocytosis and attenuated abdominal aortic aneurysm (AAA) formation in mice [56]. RvD1, RvD5 and MaR1 reduced PGE_2-induced contractile responses in human coronary arteries, suggesting beneficial effects of SPMs in CAD [57]. RvD2 treatment improved cardiovascular function, decreased fibrosis, reduced infiltration

of neutrophils, and shifted macrophages to a pro-resolving phenotype in hypertension associated cardiovascular damage in mice [41]. Also, RvD2 has shown to prevent endothelial dysfunction in obese hypertensive mice [58].

Endothelial damage resulting from vascular interventions such as balloon angioplasty or bypass graft can also induce an inflammatory response in the blood vessel. This response activates VSMC to differentiate into a proliferative phenotype and induce their migration, leading to neointimal hyperplasia and vascular restenosis, causing vascular remodeling. RvD1 and RvD2 reduced VSMC proliferation and migration upon vascular injury in a rabbit model of arterial angioplasty [59]. Similarly, RvD2 and MaR1 decreased vascular hyperplasia and reduced VSMC proliferation in a mouse model of carotid artery ligation [60]. Intravenous administration of both RvD1 and PD1 improved vascular remodeling in the rat carotid artery balloon injury model via NF-κB pathway inhibition [61]. Also, a synthetic RvD1 analogue was demonstrated to reduce neointimal hyperplasia in a rat model of balloon angioplasty [62]. In another study, oral administration of RvD1 ameliorated inflammation but not intimal hyperplasia in a rat model of carotid angioplasty [63]. Time-dependent changes of lipid mediator biosynthesis and SPM receptor expression in plasma, leukocytes, and artery walls following acute vascular injury were reported in a recent study [64]. A study from our laboratory showed that RvE1, RvD1 and MaR1 reduce the contractile response induced by TXA_2 receptor (TP) agonist U46619 in human saphenous vein (SV) [65], suggesting beneficial effects of SPMs in graft vasospasm. 15-LOX is implicated in cardiac ischemia-reperfusion (IR) injury [66]. RvD1, both free fatty acid and liposome form, demonstrated cardioprotective effects by attenuating neutrophil recruitment, and stimulating macrophage clearance post-myocardial infarction (MI) in mouse coronary artery ligation model [67]. Overall, these findings suggest that SPMs play a key role in resolution of inflammation and restoring vascular homeostasis.

4. Lipoxygenase-Driven Specialized Pro-Resolving Lipid Mediators

SPM Biosynthesis

After the pro-inflammatory phase, inflammation is resolved through an active process. The transition from initiation to the resolution phase of inflammation is a process characterized by a lipid mediator class switch. In the early phase of acute inflammation, the biosynthesis of pro-inflammatory mediators (e.g., PGs and LTs) occurs. Subsequently, these pro-inflammatory mediators are replaced by SPMs, that limit leukocyte infiltration and initiate the resolution phase [68]. Pro-resolving lipid mediators are synthesized from omega-3 PUFAs such as EPA and DHA, and from the omega-6 PUFA AA (Figure 4). This synthesis process is mediated by lipoxygenases such as 5-LOX, 12-LOX and 15-LOX [69–71]. Pro-resolving lipid mediators are classified into four main families: lipoxins, synthesized from AA; and resolvins, maresins, and protectins, synthesized from EPA and DHA [68]. SPMs can also be synthesized from n-3 docosapentaenoic acid (n-3 DPA), forming a distinct family of n-3 DPA-derived SPMs [72–75]. SPMs exhibit their pro-resolving effects through GPCRs, including ALX/FPR2, GPR32, GPR18, ChemR23, GPR37, GPR101 and LGR6 [76–78]. All have effects on various immune cells, such as neutrophils, monocytes, macrophages, dendritic cells, and also on endothelial cells [79]. SPMs enhance phagocytosis of apoptotic cells by macrophages and suppress pro-inflammatory functions by regulating cytokine and chemokine signaling and also promote the resolution of inflammation by increasing polarization of macrophages towards a resolutive (M2) phenotype [79,80].

LXA_4 is an anti-inflammatory and pro-resolving lipid mediator, promoting resolution processes such as the inhibition of leukocyte chemotaxis through its receptor, formyl peptide receptor 2 (ALX/FPR2) [81]. Lipoxins can be formed by the sequential action of 15-LOX and 5-LOX enzymes where 15-LOX oxygenates AA to produce the intermediate product, 15S-hydroperoxyeicosatetraenoic acid (15S-HpETE). This intermediate product is transferred to leukocytes, where it undergoes a second oxygenation by 5-LOX to form 5S,6S-epoxy-15S-HETE. The hydrolysis of this epoxide intermediate yields LXA_4 or LXB_4 [82]. LTA_4 can also be oxygenated by 15-LOX, or by platelet 12-LOX, leading to the formation of lipoxins. 5-LOX in neutrophils oxidizes AA to form 5S-HpETE. This intermediate is further dehydrated by 5-LOX to form LTA_4. LTA_4 is oxygenated by 15-LOX to form the intermediate product 5S,6S-epoxy-15S-HETE, which is subsequently hydrolyzed to form LXA_4 or LXB_4. As an alternative to this metabolism, LTA_4 can be transferred to platelets, where it can be further converted to LXA_4 or LXB_4 by 12-LOX [83]. Lipoxins can also be generated by the action of aspirin. Aspirin acetylates COX-2 in endothelial cells leading to the formation of 15R-HETE from AA [84], that is subsequently converted by leukocyte 5-LOX into ATL, 15-epi-LXA_4 or 15-epi-LXB_4 [26]. ATL, together with their 15(S)-related stereoisomers, inhibit neutrophil infiltration into sites of infammation, restore endothelial barrier function, direct macrophages toward the phagocytosis of apoptotic neutrophils and cellular debris, and promote the restoration of tissue homeostasis [26].

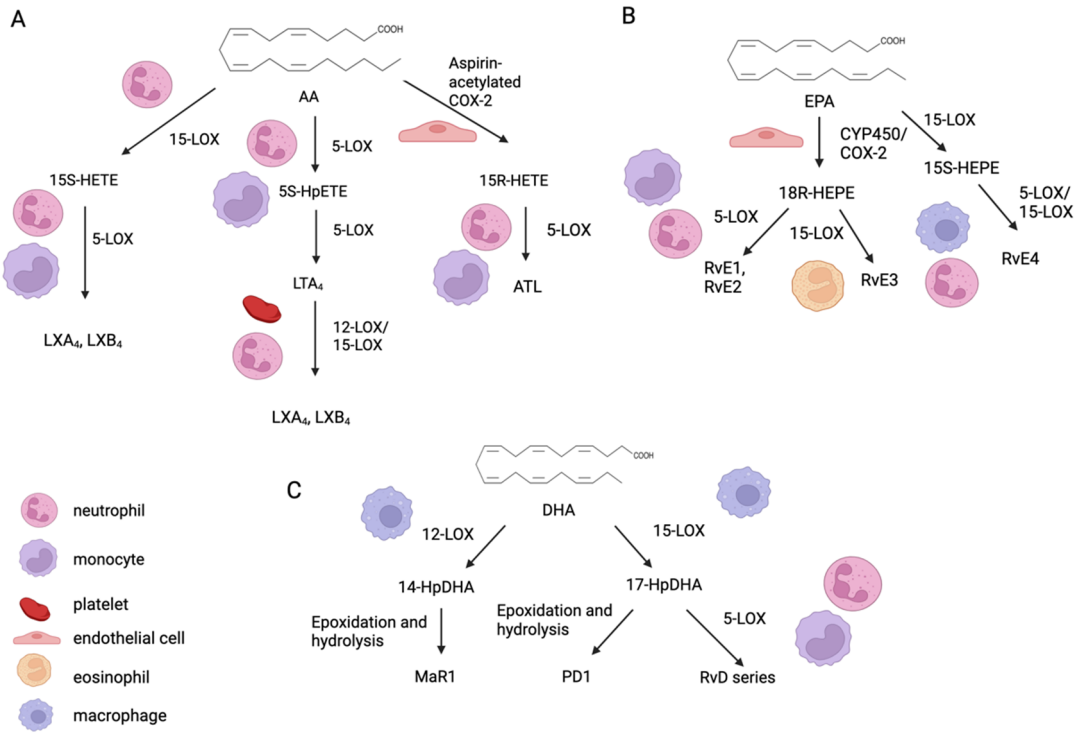

Figure 4. Summary of SPM biosynthesis pathways from PUFAs. (**A**) Summary of SPM biosynthesis pathways from AA. (**B**) Summary of SPM biosynthesis pathways from EPA. (**C**) Summary of SPM biosynthesis pathways from DHA.

RvE1 promotes the resolution of inflammation via its receptor ChemR23 that is expressed in immune cells such as macrophages and dendritic cells [51,85]. It is also highly expressed in VSMC and plays an important role in maintaining VSMC functions such as proliferation and contraction [86]. E-series resolvins are formed by the oxidation of EPA via aspirin-acetylated COX-2 or cytochrome P450 (CYP450). During this process, an intermediate called 18R-hydroperoxy-eicosapentaenoic acid (18R-HpEPE) is formed, which is further converted into an active metabolite, 18R-HEPE by the peroxidase activity. Lipoxygenation of 18R-HEPE by 5-LOX via leukocyte-endothelial interactions leads to the formation of RvE1 or RvE2 [87,88]. Alternatively, 18R-HEPE can undergo lipoxygenation by 15-LOX to form RvE3 by eosinophils [89]. EPA can also be lipoxygenated by 15-LOX to form 15S-HEPE. Subsequent lipoxygenation of this intermediate by 5-LOX or 15-LOX leads to the formation of RvE4 [7,90,91].

D-series resolvins are generated from DHA via two sequential lipoxygenase steps. First, DHA is converted to 17S-hydroperoxydocosahexaenoic acid (17S-HpDHA) by the action of 15-LOX and subsequently converted to RvD1, RvD2 or RvD5 by the action of 5-LOX [58,92]. Alternatively, the second lipoxygenation by 5-LOX forms RvD3, RvD4 or RvD6 [93]. Aspirin-acetylated COX-2 in endothelial cells can metabolize DHA into 17R-HpDHA, which is subsequently converted to aspirin-triggered RvD series (AT-RvD) by 5-LOX [94]. Two specific GPCRs, ALX/FPR2 and GPR32, have been identified for RvD1 where GPR32 and ALX/FPR2 can bind to various other SPMs in addition to RvD1, including RvD3, RvD5 and LXA_4 [23].

The biosynthetic pathways of the RvD n-3 series ($RvD1_{n-3}$, $RvD2_{n-3}$ and $RvD5_{n-3}$) derived from n-3 DPA largely parallel the 15-LOX pathway involved in synthesizing RvD1, RvD2, and RvD5 from DHA. In this pathway, 15-LOX and 5-LOX catalyze the formation of $RvD5_{n-3}$ from n-3 DPA in the presence of peroxidase [73]. Alternatively, 17S-HpDPA, produced by 15-LOX, is dehydrated by 5-LOX to form an epoxide intermediate, which is further hydrolyzed to form $RvD1_{n-3}$ and $RvD2_{n-3}$ [72]. 13-series (T-series) resolvins (RvTs) are also generated from n-3 DPA. n-3 DPA is converted via endothelial COX-2 to 13R-HpDPA, which is reduced to 13R-HDPA that is in turn converted to RvT1 by LOX action [95].

The biosynthesis of PD1 from DHA occurs in leukocytes via the 15-LOX pathway [96]. In this pathway, DHA is oxygenated and forms the intermediate 17S-HpDHA. Subsequently, 17S-HpDHA is dehydrated by 15-LOX to form 16S,17S-epoxy-DHA. This intermediate is hydrolyzed by epoxide hydrolase to yield PD1 and PD2 [96]. PD1 is also referred to as neuroprotectin D1 (NPD1). NPD1 has neuroprotective activity in brain IR injury and in retinal pigment epithelial cells exposed to oxidative stress. It can also protect cells from oxidative

stress induced apoptosis [97]. Protectins inhibit inflammation by exerting effects on neurons, immune cells, and glial cells. NPD1 mediates macrophage phagocytosis and supports the resolution of inflammatory pain [98]. In the COX-2 pathway, DHA is oxygenated by endothelial COX-2 to form the intermediate 17R-HpDHA. 17R-HpDHA is then converted to the epoxide intermediate 16R, 17R-epoxy-DHA. This intermediate is further hydrolyzed by epoxide hydrolase to form aspirin-triggered PD (AT-PD) [26]. The biosynthesis of $PD1_{n-3}$ and $PD2_{n-3}$ from n-3 DPA is catalyzed by the same enzyme groups that catalyze the formation of PD1 and PD2 from DHA [75,80]. DHA can also be converted to protectin DX (PDX) via LOX pathways [99,100].

MaR1 is synthesized via a pathway mediated by 12-LOX from DHA [69,101], and regulates tissue inflammation by modulating the leucine-rich repeat-containing G protein-coupled receptor 6 (LGR6) [102,103]. MaR1 exerts effects on dendritic cells and macrophages, regulatory T cells, and neutrophils. In addition to its anti-inflammatory properties, it also has inhibitory effects on neutrophil migration and cytokine production [104]. MaRs are synthesized via a pathway mediated by 12-LOX from DHA, which involves the formation of a 14-hydroperoxide intermediate. This intermediate can be reduced to 14-HDHA or undergo enzymatic epoxidation to form 13S,14S-epoxy-maresin. This epoxide can subsequently undergo enzymatic hydrolysis to form MaR1 or, depending on soluble epoxide hydrolase activity, form MaR2 [101]. 13S,14S-epoxy-maresin can be converted to MCTR1 (maresin conjugates involved in tissue generation) by LTC_4S [105]. The synthesis of $MaR1_{n-3}$ and $MaR2_{n-3}$ from n-3 DPA follows the same pathway as the enzymatic steps in the synthesis of MaR1 and MaR2 from DHA [74]. LOX enzymes can also form maresin-like lipid mediators (MaR-Ls) from DHA. DHA is converted to 14S-HpDHA via 12-LOX or 15-LOX, and further converted to 14S-HDHA via peroxidase reduction. 14S-HDHA is converted to 14,22-dihydroxy-docosahexaenoic acid (14S,22-diHDHA) by oxidation catalyzed by CYP450. This compound is called MaR-L1 [106]. Alternatively, when DHA is converted to 14R-HDHA by CYP450, the intermediate is further converted to 14R,22-diHDHA by CYP450. This compound is called MaR-L2 [106].

5. Evidence from Recent Experimental and Clinical Studies

Based on these mechanisms, recent studies have investigated the role of LOX-derived mediators in vascular diseases. LTs have been implicated in vascular pathologies [107,108], with several studies showing beneficial effects through targeting LT synthesis (Table 2). Recently, increased concentrations of LTE_4 and LTB_4 were shown to be associated with the impairment of vascular and endothelial function [109]. BIIL284, a LTB_4 receptor antagonist, reduced atherosclerosis in mice [4]. Montelukast, a selective cysLT1 antagonist used in asthma, was demonstrated to be protective in a mouse model of AAA [11]. Also, several studies showed beneficial effects through inhibition of LOX enzymes and FLAP in vascular diseases (Table 2). Increased 12(S)-HETE levels have been observed in patients with CAD [13]. 12-LOX inhibitor ML355 inhibited thrombus formation in mice [35]. Licofelone, a dual COX/5-LOX inhibitor has shown to attenuate intima thickening and reduce vascular inflammation in a rabbit model of atherosclerosis [110]. 5-LOX inhibitor atreleuton reduced plaque progression in patients with acute coronary syndrome (ACS) in a phase II clinical trial [111]. In a clinical study, FLAP inhibitor DG-031 reduced C-reactive protein levels in MI patients who carry at-risk variants in the FLAP or LTA_4H genes [112]. FLAP inhibitor AZD5718 has been developed for the treatment of CAD [113,114], and was reported to decrease LT levels in patients with CAD and recent MI in a phase II clinical trial [115]. However, the treatment did not result in a significant improvement in coronary microvascular function [115].

Most recent studies have demonstrated that leukocytes, such as neutrophils and macrophages, can produce SPMs such as RvE2, RvE4 and RvD5 *in vitro* [7,30,69,116]. A recent study on the modulation of lipid mediator pathways in human macrophages has shown that FLAP and 5-LOX inhibitors reduced LTs in M1 but less so in M2 macrophages. Moreover, the 5-LOX inhibitor zileuton blocked resolution-initiating SPM biosynthesis, whereas FLAP inhibition increased SPM levels in human macrophages. Furthermore, inhibition of 15-LOX suppressed SPM formation in M2 macrophages [117].

Various studies have demonstrated that SPMs can modulate vascular functions. For example, RvE1, RvD1 and RvD2 inhibited vasoconstrictor responses induced by the TP agonist U46619 in human pulmonary arteries and rat aorta [118]. We showed that RvE1, RvD1 and MaR1 reduced the contractile responses induced by U46619 in human saphenous vein *in vitro* [65]. Furthermore, RvD1, RvD5 and MaR1 reduced vasoconstriction induced by PGE_2 in human coronary artery *in vitro* [57]. SPMs have been shown to have protective effects in a number of vascular pathologies [119–121]. The RvD1/LTB_4 ratio was reported to be decreased in human vulnerable atherosclerotic plaques, and RvD1 treatment promoted plaque stability *in vivo* in a mouse model of atherosclerosis [8]. RvE1 attenuated atherogenesis *in vivo* in animal models of atherosclerosis [122,123]. LXA_4 inhibits foam cell formation in human monocytes [51], while RvD4 reduced thrombus formation in mouse deep vein thrombosis [53], and homeostatic effects of MaR1 was demonstrated in human platelets *in vitro* [32].

Deficiency in SPMs has been reported in patients with vascular diseases [124,125]. Several clinical studies have shown that supplementation of SPM precursors have beneficial effects in vascular pathologies (Table 2). Omega-3 PUFA supplementation reduced LTB_4 and improved endothelial function after acute myocardial infarction in a clinical study [126]. Supplementation of icosapent ethyl, an EPA ethyl ester, decreased the risk of ischemic events, including cardiovascular death, in patients with statin therapy [127]. A more recent study has shown that statin+icosapent ethyl caused atherosclerotic plaque regression over 18 months [128]. In healthy participants, SPM-enriched fish oil supplementation increased plasma SPM concentration in a dose-dependent manner [129], whereas in another study, supplementation of different doses of EPA+DHA resulted in a dose-dependent increase in the plasma concentrations of SPM precursors, although SPMs were not detected [130]. Supplementation of both marine oils and mono-hydroxylated SPM precursors, such as 17-HDHA and 18-HEPE, in peripheral artery disease (PAD) patients caused a shift in lipid profile favoring SPM over PG [131]. Patients with PAD showed increased plasma RvE3 after 3 months supplementation with EPA+DHA [132], while the addition of a carboxylic acid formulation of EPA and DHA, in statin-treated patients at high cardiovascular risk, resulted in no significant difference in major adverse cardiovascular events [133].

Table 2. LOX-based treatment approaches in vascular diseases.

LOX-Based Treatment	Vascular Disease	Ref.
LTB_4 receptor antagonism	Atherosclerosis	[4]
CysLT1 receptor antagonism	Aortic aneurysm	[11]
FLAP inhibition	Coronary artery disease, myocardial infarction	[115]
12-LOX inhibition	Thrombosis	[35]
COX/5-LOX inhibition	Atherosclerosis	[110]
5-LOX inhibition	Acute coronary syndrome	[111]
Supplementation of SPM precursors	Atherosclerosis, Myocardial infarction, Peripheral artery disease	[126–128,131,132]

6. Therapeutic and Translational Perspectives

The involvement of the 5-LOX pathway in the pathogenesis of inflammatory diseases is well established, and 5-LOX inhibitor zileuton and LT receptor antagonists such as montelukast are used in the treatment of asthma and allergic diseases. Alterations in the expression of 5-LOX plays a role in the pathogenesis of vascular diseases such as atherosclerosis. Upregulation of 5-LOX expression has been reported in atherosclerotic plaques [4,93]. Emerging evidence indicate that LTB_4 and CysLTs contribute to the pathogenesis of vascular diseases such as atherosclerosis and aortic aneurysm [4,11]. Also, 12-LOX and 15-LOX have shown to be involved in vascular pathologies such as atherosclerosis [12], CAD [13], and thrombosis [35]. Moreover, increased 12(S)-HETE levels have been observed in patients with CAD [13].

Treatment approaches such as LOX inhibitors, LT receptor antagonists and FLAP inhibitors [4,134–136] have been investigated in vascular pathologies. FLAP inhibition decreased LT levels in patients with CAD and MI without improvement in coronary microvascular function [115]. Furthermore, anti-inflammatory effects have been demonstrated with FLAP inhibition in MI patients who carry at-risk variants in the FLAP or LTA_4H genes, suggesting that future directions may require more precise patient selection [112]. Moreover, lipoxin and resolvin formation by the 15-/5-LOX pathway as well as by the 12-/5-LOX pathway have shown to be FLAP-dependent [28], while another study showed that FLAP inhibition does not affect the synthesis of SPMs from DHA [19]. Dual role of LOX enzymes and involvement of FLAP in the biosynthesis of both LTs and SPMs suggest the need for therapeutic strategies that selectively enhance SPM production.

Deficiency in SPMs has been reported in vascular diseases such as CAD [124]. Moreover, altered LT/SPM ratio was linked to a decrease in plaque stability in atherosclerosis [9]. Taken together, these findings suggest that SPMs could serve as biomarkers of unresolved inflammation in vascular diseases such as atherosclerosis and CAD. Studies using *in vitro* assays and animal models have demonstrated that SPMs have inflammation resolving actions in vascular pathologies such as atherosclerosis, thrombosis and AAA [49,53,56], as well as in vascular injury [59,60]. These experimental findings have generated interest in the application of pro-resolving strategies in clinical settings. Supplementation of SPM precursors in adjunct to statin therapy, decreased the risk of ischemic events and caused plaque regression in atherosclerosis patients [127,128], suggesting that combining SPM based-therapies with statin may provide additional benefits in the management of atherosclerosis. Also, aspirin can trigger alternative biosynthesis pathways generating SPMs [26], which might provide additional anti-inflammatory effects promoted by antiplatelet aspirin treatment. Studies have shown that omega-3 PUFA supplementation results in increased plasma SPM levels and beneficial effects in vascular diseases. Supplementation with EPA+DHA resulted in

increased plasma SPM in patients with PAD [132]. Increased intake of EPA+DHA improved endothelial function after myocardial infarction [126]. Given the evidence of diverse supplementary studies, modulating the levels of SPMs by omega-3 PUFA supplementation might provide beneficial effects in the management of vascular diseases such as MI and PAD. However, the physiological relevance of the effects of SPMs depends on their endogenous concentration *in vivo*. The translational potential of SPM-based therapies is constrained by the comparatively low endogenous production of these mediators in humans. *In vitro* studies showed only RvE2, RvE4 and RvD5 production by leukocytes and in much lower amounts compared to the LTs [6]. These findings highlight the need for further investigations regarding the physiological relevance of these lipid mediators *in vivo.*

7. Conclusions & Future Directions

Overall, LOX pathways have a complex and dual role in vascular inflammation. In conclusion, LOX pathways play key role in inflammatory processes through formation of lipid mediators. The action of LOX enzymes produces both LTs and SPMs, which have important functions in the regulation of the initiation and resolution of inflammation. By regulating the cellular interactions in blood vessels, these lipid mediators play an important role in vascular inflammation. Therapeutic strategies targeting LOX enzymes, FLAP and LTs or enhancing resolution by SPMs are currently being investigated in cardiovascular diseases. However, further research is needed to elucidate cell-type specific variations in LOX pathway regulation under both physiological and pathological conditions. Enhanced analytical methodologies for precise quantification of SPMs in human tissues will be essential for assessing their therapeutic significance. Further studies on the roles of LOX pathways and LOX-derived lipid mediators will help to develop LOX-based therapies in vascular diseases. Targeting LOX-based therapies to patients with impaired resolution capacity may optimize both their effectiveness and specificity. Overall, current evidence suggests that LOX pathways are closely involved in the regulation of both vascular inflammation and its resolution, presenting a novel avenue in the treatment of cardiovascular diseases.

Author Contributions

G.T.: conceptualization; S.S., M.S.A., G.O.Y. and G.T.: writing—original draft preparation; G.T., G.O.Y. and M.R.D.: writing—reviewing and editing; S.S. and M.S.A.: visualization; G.T.: supervision. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

List of Abbreviations

LOX	Lipoxygenase
AA	Arachidonic acid
LT	Leukotriene
SPM	Specialized pro-resolving lipid mediator
PUFA	Polyunsaturated fatty acid
FLAP	5-LOX-activating protein
EPA	Eicosapentaenoic acid

DHA	Docosahexaenoic acid
CAD	Coronary artery disease
TGF-β	Transforming growth factor-β
miRNA	microRNA
5-HPETE	5-Hydroperoxyeicosatetraenoic acid
LTA_4	Leukotriene A_4
cPLA2	cytosolic phospholipase A2
LTA_4H	LTA_4 hydrolase
LTC_4S	LTC_4 synthase
cysLT	Cysteinyl leukotriene
GPCR	G protein-coupled receptor
VSMC	Vascular smooth muscle cell
15-HETE	15-Hydroxyeicosatetraenoic acid
18-HEPE	18-Hydroxyeicosapentaenoic acid
17-HDHA	17-Hydroxydocosahexaenoic acid
LXA_4	Lipoxin A_4
COX-2	Cyclooxygenase-2
ATL	Aspirin-triggered lipoxin
RvE	E-series resolvins
RvD	D-series resolvins
TXA_2	Thromboxane A_2
PD	Protectin
MaR	Maresin
LDL	Low-density lipoprotein
cAMP	cyclic AMP
Ca^{2+}	Calcium
NF-κB	Nuclear factor-kappa B
ChemR23	Chemokine-like receptor 1
IL-8	Interleukin-8
MCP-1	Monocyte chemoattractant protein-1
TNF-α	Tumor necrosis factor-α
PGE_2	Prostaglandin E_2
AT-LXA_4	Aspirin triggered lipoxin A_4
NO	Nitric oxide
ROS	Reactive oxygen species
oxLDL	Oxidized low-density lipoprotein
MERTK	MER proto-oncogene tyrosine kinase
Rho A	Ras homolog family member A
AMPK	AMP-activated protein kinase
AAA	Abdominal aortic aneurysm
TP	Thromboxane A_2 receptor
SV	Saphenous vein
IR	Ischemia-reperfusion
MI	Myocardial infarction
DPA	Docosapentaenoic acid
FPR2	Formyl peptide receptor 2
15S-HpETE	15S-Hydroperoxyeicosatetraenoic acid
CYP450	Cytochrome P450
18R-HpEPE	18R-Hydroperoxy-eicosapentaenoic acid
17S-HpDHA	17S-Hydroperoxydocosahexaenoic acid
RvT	T-series resolvins
NPD	Neuroprotectin D
PDX	Protectin DX
LGR6	Leucine-rich repeat-containing G protein-coupled receptor 6
MCTR	Maresin conjugates involved in tissue generation
MaR-L	Maresin-like lipid mediator
ACS	Acute coronary syndrome
PAD	Peripheral artery disease

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