HHS Public Access

Author manuscript

Prog Lipid Res. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Prog Lipid Res. 2019 January ; 73: 28–45. doi:10.1016/j.plipres.2018.11.001.

Emerging role of 12/15-Lipoxygenase (ALOX15) in human pathologies

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Abstract

12/15-lipoxygenase (12/15-LOX) is an enzyme, which oxidizes polyunsaturated fatty acids, particularly omega-6 and −3 fatty acids, to generate a number of bioactive lipid metabolites. A large number of studies have revealed the importance of 12/15-LOX role in oxidative and inflammatory responses. The in vitro studies have demonstrated the ability of 12/15-LOX metabolites in the expression of various genes and production of cytokine related to inflammation and resolution of inflammation. The studies with the use of knockout and transgenic animals for 12/15-LOX have further shown its involvement in the pathogenesis of a variety of human diseases, including cardiovascular, renal, neurological and metabolic disorders. This review summarizes our current knowledge on the role of 12/15-LOX in inflammation and various human diseases.

1. INTRODUCTION

Polyunsaturated fatty acids (PUFAs) and their metabolites play an essential role in normal cellular growth and development (1). Arachidonic acid (AA), an essential PUFA, serves as a major precursor for eicosanoids, which in addition to their role in various physiological functions are involved in many diseases, including, atherosclerosis, diabetes and neurological disorders (2–4). Phospholipases, particularly phospholipase A_2 play a major role in the release of AA from the cell membrane in response to various cytokines, growth factors and hormones (5,6). AA is metabolized by three families of enzymes, namely cyclooxygenases, lipoxygenases and cytochrome P450 monooxygenases or epoxygenases producing prostaglandins, hydroperoxyeicosatetraenoic acids and epoxyeicosatrienoic acids, respectively (6,7). Lipoxygenases (LOXs) are non heme-iron containing dioxygenases that catalyze the stereospecific oxygenation of polyunsaturated fatty acids in lipids containing a (1-cis, 4-cis)-pentadiene moiety to the corresponding hydroperoxy derivatives (7,8). As shown in Table 1, there are six known functional LOX genes in humans (*ALOX5*, *ALOX12*, *ALOX12B*, *ALOX15*, *ALOX15B*, *ALOXE3*), four pseudogenes (*ALOX15P1, ALOXE3P1, ALOX12P1*, *ALOX12P2*), and an ALOX12 antisense gene (*ALOX12AS1*) which are

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termed by convention as “ALOX”, for arachidonic acid lipoxygenase (9). All of the ALOX genes are successively arranged within the gene cluster and do not overlap each other. The *ALOX12P2* pseudogene partly overlaps with the *ALOX12-AS1* gene and the protein coding by *ALOX12* gene is completely surrounded by the *ALOX12-AS1* gene. Another *ALOX15* pseudogene (ALOX15P2) has been detected on chromosome 9. All of these genes are located on the short arm of chromosome 17, except *ALOX5*, which is located on chromosome 10 (9–13). The mouse has seven functional LOX genes (orthologs of all human functional genes plus *Alox12e*, which is an ortholog of human pseudogene *ALOX12P2*). In mouse, almost all of these genes are located on the orthologous region of chromosome 11, except *Alox5*, which is located on chromosome 6 (9–13). LOXs are lipid-peroxidizing enzymes, categorized with respect to the their positional specificity of arachidonic acid oxygenation (7). For example, 12-LOXs is an enzyme where the digit indicates the number of carbon atom of arachidonic acid at which oxygen is inserted. The classification is simple and easy, but with increasing diversity of the LOX family it has become more confusing. In most of the mammalian species, there are several types of 12-LOX (platelet-type 12-LOX, leukocyte-type 12-LOX or epidermal type 12-LOX) and each of them is encoded by a different gene with very low phylogenetic relatedness (7). In addition, orthologues of the same gene have different reaction specificities in different species, for example human 15-LOX type 2 (ALOX15B) inserts oxygen exclusively at carbon atom 15 whereas the murine orthologue has 8S-lipoxygenating activity (14,15). The human reticulocyte type 15-LOX1 (ALOX15) produces predominantly 15(S)-HETE and only little amounts of 12(S)-HETE (ratio of 9:1), while its murine orthologue leukocyte-type 12-LOX (encoded by *ALOX15* gene), produces small amounts of 15(S)-HETE and primarily 12(S)-HETE (ratio of 1:3). Both these enzymes share 73% amino acid similarity, a similar expression pattern and largely overlap in their known biological effects (10,11,14). Recently, it has been suggested that various LOX isoforms should be named according to their encoding genes, such as all 12/15-LOX orthologs from different species should be called as ALOX15. The purpose of this review is to refresh our understanding on the role of 12/15-LOX (ALOX15) in the pathogenesis of various diseases.

2. BIOCHEMISTRY OF 12/15-LIPOXYGENASE

2.1. Expression of 12/15-lipoxygenase

12/15-LOX is constitutively expressed in reticulocytes, eosinophils, dendritic cells, alveolar macrophages, airway epithelial cells, immature dendritic cells, vascular cells, resident peritoneal macrophages, pancreatic islets and uterus (12,13,16,17). Human and mouse peripheral blood monocytes do not express 12/15-LOX in circulation, but its mRNA and protein expression can be induced in vitro by IL-4 and IL-13 in both human monocytes and murine macrophages (19–21). In human umbilical vein endothelial cells, IL-4 induces the expression of 12/15-LOX mRNA, but not active enzyme (22). Human immature red blood cells constitutively express 12/15-LOX, but erythrocytes of various species including human fail to do so (16). It has also been shown that experimental anemia in rabbit, rat and mice induces the expression of 12/15-LOX in immature red blood cells (23, 24). Human B- and T-lymphocytes do not express 12/15-LOX enzyme at high levels as indicated by RT-PCR and activity assays (25). Recently, it was shown that while human eosinophils express large

amounts of ALOX15 but not ALOX15B, neutrophils express ALOX15B but not ALOX15 (26).

2.4. Metabolites of 12/15-lipoxygenase

The physiological substrates for human and rodent 12/15-LOX enzymes are linoleic acid, alpha-linolenic acid, gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid when presented not only as free acids but also when incorporated as esters in phospholipids, glycerides, or cholesteryl esters (27) (Figure 2). 12/15-LOX metabolizes arachidonic acid to form 15(S)-hydroperoxyeicosatetraenoic acid (15(S)-HPETE) and 12(S)-hydroperoxyeicosatetraenoic acid (12(S)-HPETE). Both 15(S)-HPETE and 12(S)-HPETE are further reduced by cellular glutathione peroxidase to their corresponding hydroxy analogs, 15-hydroxyicosatetraenoic acid (15(S)-HETE) and 12-hydroxyeicosatetraenoic acid (12(S)-HETE), respectively (28,29). As shown in Table 2, both 15(S)-HPETE and 15(S)-HETE bind to and activate the Leukotriene B4 receptor 2, peroxisome proliferator-activated receptor γ (PPAR©), and at high concentrations cause cells to generate toxic reactive oxygen species (30). In these studies the concentration of HETEs required to activate were very high (10-raising a question on the physiological relevance of these findings. The endogenous levels of HETEs in different tissues or body fluids are in nM concentrations (31,32). Therefore, keeping this in mind, the interpretations of various studies should be exerted with caution. 12(S)-HPETE and/or 12(S)-HETE, bind and activate G protein-coupled receptor 31, (GPR31) and Leukotriene B4 receptor 2 (BLT2) (33). 15(S)-HPETE and 15(S)-HETE are further metabolized to various bioactive products such as lipoxins, hepoxillins, eoxins, 8(S),15(S)-diHETE, 5(S),15(S)-diHETE and 15-oxo-eicosatetraenoic acid (15-oxo-ETE). Lipoxin (LX) A4, LXB4, aspirin-triggered (AT)-LXA4, and AT-LXB4 are a class of anti-inflammatory agents that contribute to the resolution of inflammatory responses and inflammation-based diseases in animal models (27). Hepoxilin (HX) isomers such as HXA3 and HXB3 contribute to the regulation of inflammatory responses and insulin secretion (34). Eoxins (eoxin C4, eoxin D4, and eoxin E4) are pro-inflammatory and contribute to severe asthma, aspirin-induced asthma attacks, and other allergy reactions (35). 8(S),15(S)-diHETE inhibits human platelet aggregation. 5(S),15(S)-diHETE and its 5-ketone analog, 5-oxo-15(S)-hydroxy-ETE are responsible for human allergic and non- allergic inflammatory responses (36). More importantly 5-oxo-ETE inhibits the growth of cultured human umbilical vein endothelial cells as well as various human cancer cell lines (37). 12(S)-HPETE and 12(S)-HETE are metabolized to hepoxilin A3 and hepoxilin B3, which are further converted to their respective tri-hydroxyl metabolites, trioxilin A3 and trioxilin B3, respectively (38). These metabolites cause vasodilation, promote pain perception, reverse oxidative stress and induce insulin secretion in various animal model systems (38).

Docosahexaenoic acid (DHA) is also a substrate of 12/15-LOX and it is converted into 14(S)-hydroxy-DHA and 17(S)-hydroxy-DHA (39). These metabolites stimulate proliferation of human breast and prostate cell lines in culture (40–43). 17(S)-Hydroxy-DHA is further metabolized to resolvin Ds (RvDs) and protectin Ds (PDs) (42, 43). These products have high potent anti-inflammatory activity. 12/15-LOX metabolizes eicosapentaenoic (EPA) acid to 12(S)-hydroxy-EPA and 15(S)-hydroxy-EPA (39). 15(S)-

HEPA inhibits 12/15-LOX-dependent production of the pro-inflammatory mediator, LTB4 in cells. 15(S)-HEPA is further metabolized to resolvin E3, a specialized proresolvin mediator with anti-inflammatory activity (44). Linoleic acid is better positioned for reaction (shorter *d(H-OH)* distances) with 12/15-LOX as compared to arachidonic acid, but the two physiological substrates of 12/15-LOX seems to have a common binding mode and have similar preference for oxygenation (45). In this context, a recent study shows that human recombinant 12/15-LOX preferentially forms 15-HETE when incubated with equimolar amount of linoleic and arachidonic acid, suggesting that 12/15-LOX prefers arachidonic acid over linoleic acid as its primary substrate (39). Murine 12/15-LOX metabolizes linoleic acid to 13(S)-hydroperoxyoctadecadienoic acid (13(S)-HpODE) and 9(S)-HpODE, which are further reduced to 13(S)-HODE and 9(S)-HODE, respectively (39). 13(S)-HODE acts through PPARs, transient receptor potential cation channel subfamily V member 1 (TRPV1), and human GPR132 receptors to stimulate a variety of responses related to monocyte maturation, lipid metabolism, and neuron activation. 9(S)-HODE is a marker for oxidative stress and contributes to the process of pain perception and atherosclerosis (46). The Table 3, enlist all the main substrates and products of 12/15-LOX with their biological activities. Various studies have shown that activated human and murine platelets and monocytes/ macrophages generate 12/15-LOX-derived esterified HETEs (47–49). It is also reported that phosphatidylethanolamine (PE) is the predominant phospholipid that is oxidized by 12/15-LOX to generate esterified HETEs (49). The activated human monocytes generate 4 esterified HETEs, particularly one acyl and three plasmalogen PE species (18:0a, 18:0p, 18:1p, 16;0p/15-HETE-PE) (49). Similarly the murine peritoneal macrophages generate equivalent 12-HETE-PEs (48). In addition, human and murine platelets generate four PE and two phosphatidylcholine (PC)-esterified 12-HETEs including both plasmalogen and acyl forms (18:0a, 18:0p, 18:1p, and 16:0p/12-HETE-PE and 16:0a/12-HETE-PC) (47,49). Phospholipid-esterified HETEs remain cell associated and a little proportion of them are transported outside the plasma membrane.

3. 12/15-LIPOXYGENASE AND INFLAMMATION

3.1. Pro- and anti-inflammatory effects of 12/15-lipoxygenase and its metabolites

The role of 12/15-LOX has been implicated in various inflammation related diseases. Increasing evidence highlights the controversial nature of 12/15-LOX in inflammation, as its metabolites have been shown both pro- and anti-inflammatory properties. 12/15-LOX metabolite 12(S)- HETE is a potent, pro-inflammatory chemoattractant for neutrophils and leukocytes (50). The pro-inflammatory role of 12/15-LOX and its metabolites 12(S)-HETE and 15(S)-HETE were demonstrated by various studies (12,51,52). It was shown that intradermal injection of 15(S)- HPETE induces inflammatory symptoms like plasma exudation in rabbits (53). In addition, it was suggested that 12/15-LOX induces the production of pro-inflammatory cytokine IL-12 in macrophages (52), although 12/15-LOX-deficient mice displayed no decrease in IL-12 production (54). It is interesting to note that LPS-induced expression of pro-inflammatory cytokines IL-6, IL-12, CXCL9, and CXCL10 was reduced by inhibition of 12/15-LOX in macrophages (55). It was also shown that 12/15-LOX metabolite 12(S)-HETE induces the expression of IL-6, TNFα, MCP1 and adhesion molecules in macrophages and vascular cells (56–58). 12(S)-HETE also plays a role in LPS-

induced pulmonary inflammation and acid- induced acute lung injury (59). Disruption of 12/15-LOX was shown to attenuate airway allergic inflammation by inhibition of proinflammatory cytokine expression (60). Furthermore, 12/15- LOX regulates the expression of pro-inflammatory eoxins in eosinophils and epithelial airway cells (61). Eoxins were shown to cause endothelial cell dysfunction and enhance vascular permeability (61). It was further demonstrated that the increased expression of some of these inflammatory molecules was dependent on nuclear factor κB activation (60,62). It is also interesting to note that overexpression of 12/15-LOX in the heart induces MCP1 expression and promotes infiltration of macrophages causing cardiac fibrosis and systolic dysfunction (50). Macrophages from asthma patients have shown increased 12/15-LOX expression and activity as compared to control macrophages and it was further reported that the levels of 15(S)-HETE increase with severity of asthma (62,63). Tissue resident macrophages were also shown higher expression of 12/15-LOX (64). A recent study has reported an induced expression of *Alox15* gene in dextran sulfate sodium (DSS)-induced colitis in wild type (WT) mice with no changes observed in other *Alox* genes (*Alox5* and *Alox15b*) (65). Furthermore, these authors have shown that genetic deletion of 12/15-LOX resulted in reduced expression of pro-inflammatory genes and intact intestinal epithelial barrier with less severe colitis (65).

Several reports demonstrate the anti-inflammatory properties of 12/15-LOX and its metabolites (66,67). It was shown that IL-4 and IL-13 induce M2 polarization along with an increase in 12/15-LOX activity (12, 68). In addition, it was demonstrated that macrophages from STAT6-deficient mice do not respond to IL-4 or IL-13 in the induction of 12/15-LOX activity, suggesting a role for STAT6 in IL-4 or IL-13-induced 12/15-LOX expression (69–73). The anti-inflammatory effect of 12/15-LOX metabolites, 12(S)-HETE and 15(S)-HETE, has been demonstrated in ischemic brain and it was further shown that these effects were dependent on PPAR© (71,74). In addition, deletion of 12/15-LOX in arthritis mice models displayed an exacerbated inflammatory joint destruction, which was accompanied with reduced levels of lipoxin A4 (75). 12/15-LOX deficiency leads to decreased protectin DX synthesis contributing to an increased neutrophil influx in a mouse model of postoperative ileus (76). Eosinophils express significant amount of 12/15-LOX and its pro-resolving mediators such as protectin D1 that serve as “stop signals” for the inflammatory response (77). The resolution of inflammation is impaired in 12/15-LOX-deficient mice and is accompanied with impaired wound healing response as well as an increased post-inflammatory fibrosis (78,79). Mechanisms by which 12/15-LOX exhibit its pro-resolving effects are not fully understood, but it may be due to its pro-resolving mediators such as lipoxins, resolvins and protectins, which exert potent and direct anti-inflammatory effects in various cell types (64,80,81). Lipoxins are generated from 15(S)-HPETE and the pro-resolving effects of lipoxins outweigh the pro-inflammatory properties of HETEs (81). Lipoxin A4 exerts its anti-inflammatory effects in several inflammatory diseases, such as nephritis, periodontitis, arthritis and inflammatory bowel disease (82). Lipoxins are also shown to attenuate adipose tissue inflammation in mice (83). Lipoxin A4 not only reduces the recruitment of neutrophils, but also promotes the infiltration of monocytes and removal of apoptotic neutrophils by macrophages (84–86). Studies employing transgenic rabbits and virus-mediated in vivo gene transfer in rats have shown that overexpression of 12/15-LOX

leads to reduced inflammation and tissue damage with increased lipoxin A4 levels (87,88). It was also shown that Lipoxin A4 exerts its anti-inflammatory functions via G protein-coupled receptor ALX (84, 89), and ALX deficient mice displayed an aggravated form of arthritis (90). In chronic airway inflammation, Lipoxin A4 promotes apoptosis of eosinophils through activation of natural killer (NK) cells and production of anti-inflammatory cytokine IL-13 (91). Protectins and resolvins are important anti- inflammatory products of 12/15-LOX. Protectin D1 blocks T cell migration and reduces TNFα and interferon γ secretion to promote T cell apoptosis (86, 92, 93). Furthermore, protectin D1 promotes ocular epithelial wound healing in concert with lipoxin A4 (78). Administration of resolvins particularly resolvin E1 (RvE1) in murine models of acute inflammation caused a reduction in neutrophil infiltration (94). It was also shown that RvE1 directly inhibits LTB4-stimulated neutrophil transmigration in vitro (95). 12/15-LOX-derived oxidized phospholipids (OxPL) were also involved in the resolution of inflammation as they disappear during the acute phase of inflammation and reappear during the resolution phase in bacterial-mediated peritonitis (95–97). In summary, it is becoming clear that 12/15-LOX and its metabolites have both pro- and anti-inflammatory effects, and some of these differential effects of the same metabolites could be due to their differential doses.

3.2. 12/15-lipoxygenase and apoptotic cell clearance

Phagocytosis of apoptotic cells (ACs) contributes to the non-immunogenic removal of autoantigens, a process that is particularly important in clearing of damaged cells and apoptotic neutrophils during the resolution of inflammation (98, 99). Impaired clearance of ACs by macrophages results in non-infectious inflammatory response and consecutive autoimmune disease (96,98,99). During inflammation, ACs are primarily cleared by tissue resident macrophages that express 12/15-LOX, whereas monocyte-derived macrophages and other immune-competent phagocytes that do not express abundant 12/15-LOX rarely participate in this phenomenon (64, 100). This selective phagocytosis is responsible for ensuring a non-immunogenic disposal of self-antigens. In addition, 12/15-LOX expression by resident macrophages actively blocks the capacity of neighboring monocyte-derived macrophages to uptake ACs (64,100). Furthermore, deletion of 12/15-LOX enables monocyte-derived macrophages to uptake ACs, which results in impaired clearance of ACs and activation of antigen-presenting cells resulting in autoimmune diseases (64,100). Along with apoptosis, a role for 15-LOX1 in SAT1 (spermidine/spermine N1-acetyltransferase 1)-induced ferroptosis has also been demonstrated in a human lung carcinoma cell line H1299 (101,102). Ferroptosis is a form of cell death that results due to an accumulation of iron-dependent lipid peroxides (102). 12/15-LOX-derived metabolites such as lipoxins promote non-inflammatory phagocytosis of ACs by macrophages. The data presented by Miller et al. and Godson et al. also indicate an AC- induced feedback loop that involves induction of 12/15-LOX in promoting the non-immunogenic clearance of dying cells by resident macrophages (68,103).

The pro- and anti-inflammatory actions of 12/15-LOX can be attributed to the complex array of metabolites formed as a result of its catalytic activity, which is tissue and species-specific. The pro- and anti-inflammatory effects of 12/15-LOX are summarized in Table 4. The various types of lipid metabolites generated in a tissue by 12/15-LOX are dependent on

substrate availability, and local metabolite concentration. The increased availability of ω−3 vs ω−6 fatty acids lead to the formation of metabolites with anti-inflammatory properties. A study showed that 17-HDHA, a metaboliote generated due to 12/15-LOX action on DHA, is more potent PPAR© agonist than DHA itself. The activation and inhibition of anti-inflammatory PPARγ is dependent on positional isomerism of 12/15-LOX products and its concentration. The complex nature of 12/15-LOX interaction with PPAR© resulting in its activation or inhibition explains the contradictory role of this enzyme as a pro- or anti-inflammatory signaling in various diseases. The apparent contradiction about the role of 12/15-LOX has also been observed in in vivo studies, where deletion or overexpression of 12/15-LOX results in either pro- or anti-inflammatory phenotype. The formation of lipoxin A4 generation via consecutive action of 12/15-LOX and 5-LOX may explain why some 12/15-LOX deficient models show anti-inflammatory effects. A study by Poeckel et al. is in line with these observations, as knockdown of 12/15- and 5-LOX in female ApoE$^{-/-}$ mice, protected it from atherosclerosis (104). As compared to female mice, male ApoE$^{-/-}$ mice developed only a few atherosclerotic lesions and deletion of both 12/15-LOX and 5-LOX has no additional effect on lesion formation in these mice. In addition to the substrate availability, nutritional overload also regulate the balance between the formation of pro- vs anti- inflammatory 12/15-LOX metabolites. Therefore, future efforts are required to understand the mechanisms that control the formation and regulation of 12/15-LOX metabolites.

3.3. 12/15-lipoxygenase and dendritic cell maturation

12/15-LOX is expressed in immature dendritic cells (DCs) and deletion or enzymatic blockade of 12/15-LOX results in enhanced maturation of human and mouse DCs (105,106). 12/15-LOX-derived metabolites not only interfere with DC maturation but also decrease the levels of CD40 and TLR2-mediated cytokine production (106, 107). Furthermore, it was shown that 12/15-LOX-mediated blockade of DC maturation depends on anti-oxidant stress response transcription factor Nrf2 activation (108, 109). These findings suggest that 12/15-LOX activity in immature DCs regulates uncontrolled immune activation. Pathogen-associated or LPS-induced activation of DCs downregulate 12/15-LOX expression and this appears to be a prerequisite for regular and efficient DC maturation. In the absence of 12/15-LOX, the enhanced DC maturation and expression of IL-23 results in an increased differentiation of IL-23-dependent Th17 T cells. Therefore, 12/15-LOX-deficient mice models are prone to the development of Th17-driven autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE), a murine model for human multiple sclerosis (106,110). It was also shown that the proresolving role of 12/15-LOX in EAE might be through the modulation of Nrf2 activity (106). Genetic deletion of Nrf2 displayed an enhanced DC maturation resulting into exacerbated EAE (108,109,111). In addition, pharmacological activation of Nrf2 decreases DC maturation and ameliorates EAE (112,113).

4. 12/15-LIPOXYGENASE AND VASCULAR DISEASES

In this section, we focus on the role of 12/15-LOX and its metabolites in hypertension, vascular wall remodeling, atherosclerosis, thrombosis and angiogenesis.

4.1. Hypertension

Various studies have reported a role for 12/15-LOX in the modulation of vascular tone and vessel wall remodeling via actions on vascular endothelium, smooth muscle cells, or both (114). Expression of 12/15-LOX was reported not only in aortic endothelial cells but also in aortic smooth muscle cells (115). In addition, Stern and colleagues have reported that angiotensin II stimulates the production of 12/15-LOX-derived HETEs in the artery and kidney (116). Since various studies employing animal models have demonstrated a role for angiotensin II in hypertension, its capacity to produce 12/15-LOX-derived HETEs can be attributed to the involvement of 12/15-LOX in the regulation of vascular tone (117). In fact, the 12/15-LOX metabolites 15(S)-HPETE and 15(S)-HETE were reported to cause both vasoconstriction and vasodilation, although the effects were dose and species dependent (114). For example, at lower concentrations 15(S)-HPETE and 15(S)-HETE exhibit vasorelaxation effects, while at higher concentrations they cause vasoconstriction (114). Furthermore, in neonatal rabbit pulmonary arteries, hypoxia induces 15(S)-HETE-dependent vasoconstriction (118). Supporting these observations, 12/15-LOX-derived metabolites 12(S)-HPETE and 15(S)-HPETE were reported to inhibit prostacyclin synthase activity, thereby decreasing the levels of vasodilator prostacyclin (116). In addition, it was suggested that 12/15-LOX reduces the bioavailability of nitric oxide, thus promoting vasoconstriction (119, 120). The vasoconstrictive responses of 12(S)-HETE were further demonstrated in dog renal arcuate arteries (121). In contrast to these observations, some reports showed that 12(S)-HETE acts as an endothelium-derived hyperpolarizing factor in rat mesenteric arteries (122), rat basilar arteries (123), porcine coronary arteries and human coronary arteries (124, 125). In human coronary arteries, 12(S)-HETE induced vascular smooth muscle cell hyperpolarization through activation of large conductance K_{Ca} (BK_{Ca}) channels resulting in relaxation (114). Although all these studies suggested a physiological role for 15(S)- HETE/ 12(S)-HETE and 13(S)-HODE in vasoconstriction and vasorelaxation, the concentrations used to observe these effects were quite high. In addition, the isomer specificity and enantioselectivity were also not tested in these studies. It was also shown that treatment of pre-constricted rabbit arterioles with AA led to vasorelaxation and the effect was endothelium dependent and the major mediators were found to be 12/15-LOX metabolites, namely, hydroxyepoxyeicosatrienoic acids (HEETA) and trioxilin A3 (126). In addition, another metabolite of 12/15-LOX which was identified as 13-hydroxy-14,15-epoxyeicosatrienoic acid (EETA) was found to mediate vasodilatory effects of AA in rabbit aorta and mesenteric arteries via acting on K(+) channels and causing smooth muscle cell hyperpolarization (127). It was also demonstrated that rat aorta treated with 12/15-LOX product of AA, trioxilin C3, undergoes vasodilation (128). In addition, 12/15-LOX metabolite hepoxilin A3 while having no direct effect on vascular tone in rat aorta and portal vein potentiated norepinephrine-induced vascular contractions in a calcium-dependent manner (129). 12/15-LOX metabolites lipoxins were also reported to promote vasorelaxation in aorta and pulmonary artery (130). In summary, the published reports indicate that 12/15-LOX pathways have multiple effects on both endothelial cells and smooth muscle cells regulating vasomotric properties of large and small arteries.

4.2. Vascular wall remodeling

The 12/15-LOX and its metabolites were involved in the remodeling of both large and small arteries. Vascular wall remodeling is an active process that occurs in response to elevated shear stress, pressure or injury (131). In vascular wall remodeling, vascular smooth muscle cells migrate from media to intima and proliferate in the intimal region leading to increased thickening of the vessel wall. Among the many cell types, the migration and proliferation of vascular smooth muscle cell is an important factor in physiologic or pathologic vessel wall remodeling (131). It was reported that 12/15-LOX plays a role in vascular smooth muscle cell migration, proliferation and apoptosis (131). Furthermore, various studies have demonstrated the involvement of 12/15-LOX metabolites in the migration and proliferation of smooth muscle cells and the mitogenic effects of 12/15-LOX were dependent on activation of MAP kinases (132, 133). Similar observations were made with 12/15-LOX metabolite of LA, namely 13(S)-HPODE in porcine vascular smooth muscle cells and the role of MAP kinases, NFκB and VCAM-1 in these responses (134, 135). Another study suggested that 13(S)-HPODE induces NFκB- dependent expression of MCP1, a potent vascular chemoattractant and mitogen (134, 135). A report also suggested that 13(S)-HODE induces intracellular calcium and cGMP production in porcine aortic smooth muscle cells (136). Furthermore, depletion of 12/15-LOX inhibited PDGFB-induced migration of porcine aortic smooth muscle cells, suggesting the role of 12/15- LOX in smooth muscle cell migration (137). It was further reported that 15(S)-HETE-dependent activation of Rho-kinases regulates hypoxia-induced rat pulmonary vascular wall remodeling (138). Studies from our laboratory have shown that 15(S)-HETE stimulates the migration of smooth muscle cells and neointimal development via cAMP-response element binding protein-mediated IL-6 expression and Src-STAT3-mediated MCP1 expression (139, 140). Furthermore, 12/15-LOX appears to be involved in cell proliferation as vascular smooth muscle cells from 12/15LOX knockout mice displayed a decreased S-phase entry (141). Finally, it was also indicated that 15(S)-HETE protects rat pulmonary arterial smooth muscle cells from apoptosis via the PI3K/Akt pathway (142). Collectively, all these studies support a role for 12/15-LOX in the regulation of smooth muscle cell migration and proliferation, and suggest its importance in active remodeling of the large and small vessels.

4.3. Atherosclerosis

Atherosclerosis, a multifactorial disease, is the foremost cause of ischemic heart disease and ischemic stroke, and is the leading cause of death and disability in the industrialized countries accounting for 25% of all cases of death (http://www.who.int/mediacentre/factsheets/fs310/en/; 143). The endothelial dysfunction, which represents the earliest changes during atherosclerotic lesion formation, increases the lipid permeability of the endothelium, macrophage recruitment, foam-cell formation and homing of T lymphocytes and platelets (144). The intimal lipid accumulation and local inflammation are closely linked to the pathogenesis of atherosclerosis and macrophages appear to play a central role in the deregulation of vessel-wall lipid homeostasis and orchestrating inflammatory responses (145). In this specific section, we will overview the role of 12/15-LOX in atherogenesis.

4.3.1. 12/15-lipoxygenase and endothelial cell dysfunction—The endothelium forms a continuous inner lining of the blood vessels and provides non-platelet adherence and

non-thrombogenic surface with selective barrier permeability between the vascular wall and blood (146, 147). In inflammatory conditions, the endothelial cells undergo phenotypic changes as characterized by the loss of their barrier function and increased leukocyte adhesion (147). Endothelial dysfunction is generally regarded as the initial step in atherosclerotic plaque formation (147). In the initial stages of endothelial dysfunction, tight junctions (TJs) between the endothelial cells are disrupted leading to increased paracelluar permeability, also known as type I endothelial cell activation (147). During the subsequent type II endothelial activation, expression of inflammatory and adhesion molecules is triggered, leading to the recruitment of monocytes/macrophages to the endothelium and their subsequent transendothelialization (147). Various studies have demonstrated the role of 12/15-LOX in high fat diet (HFD)-induced endothelial cell (EC) barrier dysfunction (148, 149). Specifically, Kundumani-Sridharan et al. observed that 15(S)-HETE, the 12/15-LOX metabolite of AA, induces EC TJ disruption and its barrier dysfunction by Src and Pyk2-dependent tyrosine phosphorylation of zonula occluden (ZO)-2 and its dissociation from Claudins 1/5, which in turn enhances transendothelialization of monocytes/macrophages (148). In addition, feeding mice with HFD induces the expression of 12/15-LOX in the aorta, disassembles ZO-2 from the endothelial TJs and increases the adhesion of circulating monocytes to the TJ-disrupted endothelium (148). Furthermore, it was reported that XO via ROS production and Src and Pyk2 activation mediates junction adhesion molecule A (JamA) tyrosine phosphorylation leading to its dissociation from occludin causing EC TJ disruption and barrier dysfunction in response to 15(S)-HETE and HFD (149). It was also shown that HFD-fed C57BL/6 mice but not 12/15-LOX knockout mice have enhanced XO expression and activity in the artery, which was correlated with increased aortic TJ disruption, barrier permeability with enhanced leukocyte adhesion, and these responses were attenuated by XO inhibitor allopurinol (149). In addition to these observations, Chattopadhyay et al. has demonstrated that 15(S)-HETE via PKCε-mediated serine/threonine phosphorylation of ZO1 induces its dissociation from occludin, disrupting EC TJ and barrier function (150). These observations provide novel insights on the role of 12/15-LOX in TJ disruption leading to increased vascular permeability and leukocyte adhesion.

4.3.2. 12/15-lipoxygenase and oxidation of lipoproteins—Oxidative modification of low-density lipoprotein (LDL) particles leads to the formation of atherogenic oxidized (ox) LDL particles. The increased presence of oxLDL particles in the arterial wall induces the expression of scavenger receptors such as SR-A and CD36 in macrophages and smooth muscle cells, which in turn facilitate the uptake of oxLDL by these cells becoming foam cells (151). Although various factors can influence the oxidative modification of LDL, many reports have shown that rabbit, mouse, porcine and human 12/15- LOX directly oxidizes LDL particles and contributes to foam cell formation (152–155). It is also interesting to note that rat ALOX15 oxygenates neither LDL nor HDL (156). Interestingly, fibroblasts transfected with 12/15-LOX cDNA have an enhanced capacity to oxidize LDL compared to control cells (157, 158). In addition, it was reported that deletion of 12/15-LOX in macrophages reduces their ability to oxidize LDL (159) and transgenic expression of 12/15-LOX resulted in enhanced IL-4 or IL-13 production and LDL oxidation (160). Retrovirus-mediated overexpression of human 12/15-LOX in rabbits has resulted in increased accumulation of oxLDL in the arteries as compared to mock-transfected animals upon

feeding with cholesterol-rich diet (161). Initially it was thought that 12/15-LOX influences LDL oxidation either by direct oxidation of esterified lipids on the LDL particles or the oxidation of free fatty acids, which are then incorporated into the LDL particles (162). In this aspect, Zhu et al. showed that after treatment of peritoneal macrophages with LDL particles, 12/15-LOX translocate from the cytoplasm to the plasma membrane and oxidizes the LDL particles (163). Furthermore, they have shown that inhibition of 12/15-LOX translocation attenuates LDL oxidation (163). Oxidation of LDL particles not only depends on 12/15-LOX translocation but also on its binding to the low density lipoprotein receptor-related protein (LRP) (163, 164) without affecting the receptor endocytosis or degradation (165). LRP stimulates both the transfer of cholesterol esters from the LDL particles to the plasma membrane and the translocation of the 12/15-LOX from the cytoplasm to the plasma membrane (164). Supporting these observations, blocking LRP function with a specific antibody inhibited 12/15-LOX translocation from the cytoplasm to the plasma membrane and cholesterol esters uptake into the membrane resulting in reduced LDL oxidation (164). However, the molecular mechanisms of LRP-mediated membrane translocation of 12/15-LOX and its involvement in LDL oxidation are not clear.

Besides LDL, 12/15-LOX oxidizes high-density lipoprotein (HDL) leading to impairment of reverse cholesterol transport. HDL is one of the smallest lipoprotein particles and transports cholesterol out of the arterial wall, reducing the burden of its accumulation in macrophages and smooth muscle cells and preventing atherosclerosis (166). Oxidation of HDL changes its lipoprotein structure and impairs its anti-atherogenic function (167,168). The 12/15-LOX oxidized HDL has a lower cholesterol accepting potential and impaired cholesterol efflux, probably due to impaired binding to the SR-B1 or ABCA1 receptors (169,170). Oxidation of HDL also leads to accumulation of unesterified cholesterol in macrophages, which is cytotoxic for cells (171). The decreased efflux of cholesterol and increased presence of unesterified cholesterol in macrophages contribute to enhanced foam cell formation and atherogenesis. It has also been reported that HDL3 modification by 12/15-LOX impairs eNOS activation and TNFα-induced inflammatory responses in endothelial cells (172, 173).

4.3.3. 12/15-lipoxygenase and CD36 expression—12/15-LOX and its metabolites can also contribute to foam cell formation via its capacity to increase the scavenger receptor CD36 expression in macrophages (174). Various reports have shown that 12/15-LOX and its metabolites 15(S)-HETE and 13(S)-HODE increase the expression of CD36 in macrophages and this effect is mediated by PPARγ (174,175). It has also been reported that 12/15-LOX increases the degradation of ATP-binding cassette transporter G1 (ABCG1) via p38 MAPK and JNK2-dependent pathways, thereby increasing the retention of cholesterol in cells (176). In addition, a recent study has shown that 12/15-LOX and its metabolite 15(S)-HETE induce the expression of CD36 in macrophages via ROS-dependent Syk and Pyk2-mediated STAT1 activation leading to enhanced CD36 expression and foam cell formation (177). In contrast to these findings, a few studies have reported that activation of PPARα by 13(S)-HODE results in increased ABCA1 expression and enhanced cholesterol efflux from macrophages, suggesting an atheroprotective role of 12/15-LOX (178, 179). Future studies are required to understand how arachidonic acid and linoleic acid metabolites of 12/15-LOX exhibit quite opposite effects on atherogenesis.

4.3.4. 12/15-lipoxygenase and monocyte recruitment—Monocyte recruitment to the intima plays an invariable role in atherogenesis (180,181). Towards this end, it was reported that mice lacking 12/15-LOX exhibits decreased monocyte accumulation in the intima reducing atherogenesis (182,183). On the other hand, transgenic mice overexpressing murine 12/15-LOX showed a two-fold increase in its metabolites and resulted in increased monocyte accumulation and fatty streak formation and these effects were blocked by 12/15-LOX inhibitors (183). In addition, treatment of endothelial cells from transgenic mice overexpressing murine 12/15-LOX with 12-HETE and 13-HODE further enhanced monocyte adhesion (183). Similar observations were reported in diabetic db/db mice, which express higher 12/15-LOX levels than wild type mice (184). Recently, we have also reported a role for 12/15-LOX metabolite 15(S)-HETE on migration and adhesion of monocytes to endothelial cells (185). They have further suggested that the 12/15-LOX metabolite, 15(S)-HETE, exacerbates atherogenesis by enhancing CREB-dependent IL-17A production (185). Various reports have shown a role for MCP1 and the adhesion molecules ICAM-1 and VCAM1 in 12/15-LOX- mediated chemotaxis and binding of monocytes to endothelial cells (183,184, 186). Interestingly, it was also shown that 12/15-LOX metabolite 12(S)-HETE increases ICAM-1 expression via activation of protein kinase Cα and NFκB (186). Recently, we have also shown that monocytes from 12/15-LOX$^{-/-}$ mice exhibited diminished migratory response, which was rescued by administration of 12(S)-HETE, in a peritonitis model (187).

4.3.5. 12/15-lipoxygenase and animal models of atherosclerosis—Various studies have reported both the pro- and anti-atherogenic role of 12/15-LOX in animal models. Mice overexpressing human 15-LOX in the endothelium were found to be more susceptible to developing atherosclerotic lesions as compared to littermate controls (188). Disruption of 12/15-LOX in ApoE$^{-/-}$ mice showed reduced atherosclerotic lesions fed with chow diet for 15 weeks to 1 year (189). Similarly, using 12/15-LOX and LDL receptor double deficient mouse, George et al. have reported a significant decrease in atherosclerotic lesion development at several time points of feeding with high fat diet (190). Consistent with these observations, Kotla et al. reported that deletion of 12/15-LOX in ApoE-deficient mice attenuates high fat diet-induced atherosclerotic lesions (185). To further identify the cell type(s) that are mediating pro-atherogenic effects of 12/15-LOX, Huo et al. have demonstrated that ApoE$^{-/-}$ mice engrafted with bone marrow from 12/15-LOX$^{-/-}$/ApoE$^{-/-}$ mice exhibited a significant reduction in atherosclerotic lesion development upon feeding with high fat diet (HFD) (191). Based on these observations, the authors have suggested that macrophages constitute the primary source of 12/15-LOX in atherogenesis (191). Presence of 12/15-LOX mRNA and protein were observed in the atherosclerotic lesions of hypercholesterolemic rabbits and were seen to be colocalized with the epitopes of oxidized LDL in the macrophage-rich lesion area (192). These observations support the hypothesis that 12/15-LOX plays an important role in LDL oxidation and atherosclerotic lesion progression. In contrast, there are several studies which indicate a rather atheroprotective role of 12/15-LOX. In a transgenic rabbit model overexpressing human 12/15- LOX in macrophages decreased atherosclerotic lesions were observed when fed with HFD (193). As these rabbits produced increased amounts of 13(S)-HODE, the authors have envisioned that the atheroprotective effects of 12/15-LOX could be due to an increased production of this

eicosanoid. Furthermore, rabbits with transient anemia showed increased expression of 12/15- LOX in reticulocytes and exhibited decreased lipid deposition in the thoracic aorta compared to controls (194). A study by Merched et al. has also demonstrated that ApoE$^{-/-}$ mice overexpressing 12/15-LOX were less prone to develop atherosclerosis and the ApoE$^{-/-}$ mice lacking 12/15-LOX show accelerated atherosclerotic lesion formation (195). In addition, transplantation of bone marrow from ApoE$^{-/-}$:12/15-LOX$^{-/-}$ but not ApoE$^{-/-}$ mice into ApoE$^{-/-}$:12/15-LOX$^{-/-}$ resulted in increased atherosclerotic lesion formation. The studies by these authors also show that 12/15-LOX protects mice from atherosclerosis via increased biosynthesis of proresolving mediators like lipoxin A4, resolvin D1 and protectin D1 (195).

4.3.6. 12/15-lipoxygenase and human atherosclerosis—The role of 12/15-LOX in human atherosclerotic lesion development is still not clear. Analyzing human atherosclerotic plaques revealed a significant increase in 12/15-LOX expression (177). Analysis of human atherosclerotic plaques showed increased levels of 13(S)-HODE compared to 13(R)-HODE, suggesting increased expression of 12/15-LOX in the lesions (196,197). However, there are a few studies, which showed an increased 12/15-LOX expression with decreased lesion severity in human clinical samples (198,199). Specifically, a polymorphism in 12/15-LOX promoter (a C to T substitution at position −292), which promotes its increased expression and activity, was found to be associated with a reduction of risk for atherosclerosis (198,199). In summary, various cell culture and animal model studies have supported a dual role for 12/15-LOX in atherosclerosis (Figure 3). In this aspect, macrophage, smooth muscle or endothelial-specific generation of 12/15-LOX knockout mice models may provide more insights into the role of 12/15-LOX and its metabolites in atherosclerosis. In addition, extending these studies to species other than rodents may clarify its differential roles in atherosclerosis. Larger genetic studies may also be needed to establish the pro- or anti-atherogenic effects of 12/15-LOX in human atherogenesis.

4.4. 12/15-lipoxygenase and thrombosis

Hemostasis and thrombosis is a highly complex and tightly regulated process that involve the formation of unstable platelet aggregate at the site of vascular injury (200). 12(S)-HETE is shown to play a role in platelet activation, granule secretion, and clot retraction suggesting its importance in platelet activation (201). It was also reported that 12/15-LOX regulates protease-activated receptor 4 (PAR4) and glycoprotein VI (GPVI)-mediated signaling in the platelets (202,203). Recently, it was also shown that selective inhibition of 12/15-LOX impairs thrombus formation and vein occlusion (204). The initiation of coagulation cascade predominantly depends on the presence of procoagulant lipid surface and tissue factor (205). In this context, it has been demonstrated that 12-HETE-PC and 12-HETE-PE enhance coagulation factor interaction with phopsholipids and tissue factor dependent coagulation (47). 12/15-LOX regulates production of procoagulant phospholipids in eosinophils and thereby mediate hemostasis and thrombosis in response to vascular injury (206). In addition, it has been reported that 12/15-LOX generated HETE-PLs were significantly higher in humans with thrombotic disorder antiphopholipid syndrome (APS) than healthy individuals (207). Furthermore, it was also demonstrated that HETE-PLs enhanced coagulation in WT

mice and restored hemostasis in 12/15-LOX$^{-/-}$ mice (207). The current efforts in this area are focused on delineating the mechanisms underlying the role of 12/15-LOX-mediated lipid oxidation in coagulation and hemostasis.

4.5. 12/15-lipoxygenase and angiogenesis

12/15-LOX and its metabolites are involved in pathological and tumor angiogenesis. Towards this end, work from various laboratories including ours has revealed that eicosanoids influence angiogenesis (Figure 4) (208–213). It was also shown that PUFAs, particularly AA, the precursor for eicosanoids, promote angiogenesis (214,215). It was shown that cytosolic phospholipase A_2 (cPLA$_2$) that liberates AA from the sn-2 position of glycerophospholipids exerts a positive effect on the regulation of angiogenesis (216). Our studies have shown that 15(S)-HETE, possesses the capacity to stimulate various signaling molecules, including Src, phosphatidylinositol 3-kinase (PI3K), Akt, MAP kinase/ERK kinase 1 (MEK1), and c-Jun N-terminal kinase 1 (JNK1) leading to activation of transcriptional factors such as activating transcriptional factor 2 (ATF2), activator protein 1 (AP1), early growth response gene 1 (Egr1) and signal transducers and activators of transcription (STATs) in influencing the expression of angiogenic molecules such as fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF) and interleukin-8 in enhancing angiogenesis (209–211, 213,217–219). Our studies have indicated that Src, a non- receptor tyrosine kinase (206) and Rac1, a Rho GTPase, are the most responsive signaling molecules activated by and involved in 15(S)-HETE-induced angiogenesis (217,219). Furthermore, our findings have provided the first direct evidence on the role of 12/15-LOX in ischemia-induced HMG-CoA reductase expression and Rac1 farnesylation (220). In addition, it was shown that overexpression of 12/15-LOX in human prostate cancer cell line increases VEGF secretion and enhances angiogenesis (221). It was also demonstrated that 12/15-LOX via HIF1α induction enhances angiogenesis in prostate tumor cells in response to hypoxia (222). The absence of glutathione peroxidase 4 induces 12/15-LOX activity and angiogenesis in subcutaneously implanted mouse tumors and pharmacological inhibition of 12/15-LOX reverses theses effects (223). These findings are ambiguous, as no attempts were made either to test the inhibitory effects of NDGA, Baicalein and PD146176 on 12/15-LOX expression/activity or their effects on other LOX isoforms. On the other hand, NDGA and Baicalein are effective anti-oxidants, and their off-target effects might have impacted the results. Recently, it has also been demonstrated that most of the 12/15-LOX inhibitors (ML351, PD146176, BLX-2481 and BLX-2477) failed to decrease 12/15-LOX activity at lower concentrations (224). Therefore, these data need to be confirmed using 12/15-LOX$^{-/-}$ mice before drawing further conclusions. Despite these observations, a few reports have shown that 12/15-LOX limits angiogenesis in some animal models. Administration of 12/15-LOX in rabbit skeletal muscle prevents the angiogenic effects of VEGF (225). The possible mechanism underlying this effect appears to be linked to its effect on reduction in NO production and VEGFR2 expression (225). In addition, Viita et al. have shown that adenoviral-mediated intravitreal delivery of 12/15-LOX gene prevents VEGF- induced corneal neovascularization in rabbits (226). Harats et al. has reported a similar finding where overexpression of 12/15-LOX prevented tumor angiogenesis (227). In addition, the metabolites of 12/15-LOX such as lipoxin A4 and its receptor were demonstrated to exert anti-angiogenic effects in a corneal neovascularization model (228).

Collectively, the role of 12/15-LOX in angiogenesis appears inconclusive and requires further investigations.

5. 12/15-LIPOXYGENASE AND DIABETES

5.1. 12/15-lipoxygenase and β-cells of the pancreatic islets

12/15-LOX and its metabolites have been implicated in diabetes (Figure 5). Blood glucose homeostasis is maintained by insulin secretion. Insulin produced by the β-cells of the pancreatic islets maintains blood glucose levels via promoting glucose uptake by muscle and adipose tissue and suppressing gluconeogenesis and promoting glycogenesis in the liver (229). In a low-dose streptozotocin-induced diabetes model, mouse deficient in leukocyte 12/15-LOX showed increased resistance to diabetes (230). Similar results were reported by a congenic 12/15-LOX knockout in non-obese diabetic (NOD) mice (231). The depletion of 12/15-LOX significantly ameliorates the development of autoimmune type 1 diabetes in NOD mice (231). Recent evidence indicates that both forms of diabetes (types 1 and 2) are associated with a significant loss of β cells (232). Gene-based knockout studies and targeted protein knockdown approaches have provided clarity on the role of 12/15-LOX in islet functions (233, 234). Studies by Nunemaker et al. and Sears et al. have shown that HFD-induced insulin resistance and impairment in islet function can be prevented by disruption of 12/15-LOX (233, 234). In addition, a study by Tokuyama et al. has reported increased expression of 12/15-LOX in diabetic Zucker rats (235). The β-cells of the pancreatic islets secretes insulin and out of the four predominant endocrine cell types (α, β, δ and F cells) present in the islets, the insulin-producing β-cells is the preferential site of 12/15-LOX expression (236–238). However, Kawajiri et al. reported that 12/15-LOX expression was colocalized with glucagon-expressing α-cells in the rat islets and overexpression of 12/15-LOX in α-cells doubles glucagon secretion (239). A few studies showed that addition of 12/15-LOX metabolites, 12(S)-HPETE or 12(S)-HETE, to human islets results in decreased islet viability and insulin secretion (240). In addition, it was shown that 12(S)-HETE induces mitochondrial oxidative stress in β-cells causing their apoptosis (241). In these studies, the authors have used physiological concentrations of 12(S)-HETE, but not tested the role of other isomers (15(S)-HETE, 5(S)-HETE, 9(S)-HETE) or its enantiomer (12(R)-HETE) on β-cell apoptosis. Due to the absence of proper control, it is hard to assess the significance of 12(S)-HETE on β-cell apoptosis and mitochondrial oxidative stress (241). It is known that mitochondrial dysfunction decreases the ATP/ADP ratio, thereby affecting insulin secretion from the pancreatic islets. However, it is important to note that while AA stimulates insulin secretion from pancreatic β-cells, 12/15-LOX inhibits it, perhaps due to a reduction in the availability of free AA (242). Recently, it was also reported that cell specific deletion of 12/15-LOX in islets results in improved insulin secretion and protection from any abnormalities in blood glucose levels due to HFD feeding (243). In addition, a substantial increase in 12/15-LOX levels were reported in pancreatic islets of 10-week old db/db prediabetic mice and the increase in 12/15-LOX levels goes in tandem with a decrease in islet number (244).

5.2. 12/15-lipoxygenase and diabetic retinopathy

Diabetic retinopathy is a serious complication of diabetes that can cause blindness (245). The role of 12/15-lipoxygenase in diabetic retinopathy is still ambiguous. In 1990s, Augustin et al. has reported elevated levels of 12/15-LOX metabolite, 15(S)-HETE, in the epiretinal membranes of patients with diabetic retinopathy (246). Later, Schwartzman et al. has found that 5-LOX product 5(S)-HETE was substantially higher in diabetic ocular vitreous with no significant changes in 15(S)-HETE levels (247). Recently, it has been reported that 12/15-LOX metabolites 12(S)-HETE and 15(S)-HETE induce microvascular dysfunction during diabetic retinopathy through NADPH oxidase-dependent mechanisms and genetic deletion of 12/15-LOX attenuated diabetes-induced endoplasmic reticulum (ER) stress in mouse retina (248–250). Furthermore, it was also reported that 5(S)-HETE, 12(S)-HETE and 15(S)-HETE are required for different stages of diabetic retinopathy (249).

5.3. 12/15-lipoxygenase and diabetic peripheral neuropathy

Diabetic peripheral neuropathy is a disease, which affects at least 50% of the patients with diabetes and is the major cause of foot amputation (251). The role of 12/15-LOX in peripheral nervous system is actively investigated and it was shown that mice fed with high fat diet have increased expression of 12/15-LOX in peripheral nerves and dorsal root ganglia (252). It was also reported that PM5011, an extract from the herb Artemisia dranunculus reduces 12/15-LOX expression and improves peripheral neuropathy in streptozotocin-induced diabetic mice (253).

5.4. 12/15-lipoxygenase and diabetic nephropathy

Diabetic nephropathy is the major cause of death in diabetic patients and there are various reports, which highlight the importance of 12/15-LOX in diabetic nephropathy (254). 12/15-LOX is present in glomeruli mesangial cells, podocytes and renal microvessels and its expression at both mRNA and protein levels increases along with established markers of diabetic nephropathy (255, 256). It was also shown that glucose increases the expression of 12/15-LOX in cultured mesangial cells (256, 257). In addition, TGF-β and angiotensin II induce the expression of 12/15-LOX in mesangial cells and pharmacological inhibition of 12/15-LOX blocks TGFβ and angiotensin II-induced mesangial cell hypertrophy and matrix accumulation (258–260). The importance of 12/15-LOX in diabetic nephropathy can also be assessed by the observations that siRNA-mediated down regulation of 12/15-LOX reduces renal dysfunction in a mouse model of type 1 diabetes (258,261).

6. 12/15-LIPOXYGENASE AND NEUROLOGICAL DISEASES

6.1. Alzheimer’s disease

Alzheimer’s disease (AD) is a chronic neurodegenerative disease characterized by progressive memory loss (262). A study by Li et al. showed that metabolic products of 12/15-LOX were significantly higher in experimental model of brain ischemia-reperfusion injury, and suggested that this enzyme may be involved in neurodegeneration (263). Later on, a study by Pratico et al. reported elevated levels of 12/15-LOX and its metabolites 12(S)-HETE and 15(S)-HETE in frontal and temporal brain regions of Alzheimer’s patients (4). In

a series of in vitro studies using neuronal cells having Swedish familial AD mutation, a widely used cellular AD model, it was found that 12/15-LOX not only regulates Ab plaque production and tau phosphorylation but also regulates AD-associated synaptic pathology and behavioral impairments (264,265). Strikingly, disruption of 12/15-LOX in transgenic AD mice model showed a significant reduction in amyloid formation with improved memory (266). In summary, 12/15-LOX appears to play a critical role in AD and could be a possible target for its therapy.

6.2. Cerebrovascular disease

Various studies have demonstrated a role for 12/15-LOX in cerebrovascular diseases (267, 268). Van Leyen et al. reported that in murine model of transient middle cerebral artery occlusion, the levels of 12/15-LOX were increased in neurons surrounding an infarct and intraperitoneal injection of baicalein, a potent inhibitor of 12/15-LOX (Table 5 enlist the known inhibitors of 12/15-LOX), reduced the infarct size (268). Decreased infarct size was also seen in 12/15-LOX knockout mice (268). Studies by Zhang et al. have shown that 12/15-LOX-mediated peroxynitrite toxicity plays an important role in neuron damage after ischemia (269). In addition, these authors have shown that inhibition of 12/15-LOX reduced zinc-induced reactive oxygen species generation and neuronal cell death (269). Furthermore, 12/15-LOX expression was observed in pre-ischemic areas of mouse brain, particularly in neurons and vascular endothelial cells after ninety minutes of cerebral artery occlusion (270). In line with these findings, inhibition of 12/15-LOX prevented ischemia-induced blood brain barrier disruption (270). They have also shown that baicalein-treated mice and 12/15-LOX knockout mice had less water content in ischemic brains (270). It was also reported that inhibition of 12/15-LOX in a rabbit model of embolic stroke reduced post-stroke deficits in behavior (271).

6.3. Parkinson’s disease

Parkinson’s disease (PD) is a degenerative neuromotor disorder of the central nervous system and 12/15-LOX appears to play an important role in this disorder (272). A study by Li et al. has demonstrated that 12/15-LOX activation is associated with a decrease in neuronal concentrations of anti-oxidant glutathione levels, an early biomarker of PD (273). It was also suggested that under glutathione depletion, nitric oxide (NO) becomes neurotoxic, particularly to the dopaminergic neurons of the midbrain in PD (274). In a subsequent study, these authors have demonstrated that inhibition of 12/15-LOX with baicalein and nordihydrogualaretic acid prevents the neurotoxic effects of NO (275). In addition, they found that addition of AA or 12(S)-HETE to cells causes neuronal toxicity in the absence of glutathione. Therefore, it can be concluded that the neurotoxity seen in PD appears to be mediated by NO/12/15-LOX, particularly under glutathione depletion.

7. 12/15-LIPOXYGENASE AND OBESITY

Obesity is a fast growing medical condition in which the excess deposition of adipose tissue can lead to reduced life expectancy and/or increased health problems (276). Approximately 34.9% (78.6 million) of adults and 17% (12.7 million) of children and adolescents aged 2–19 years in U.S. are obese, with an estimated annual medical cost of $147 billion (277, 278).

It has been shown that mice fed on high fat diet have increased 12/15-LOX activity in white adipocytes and this increase in 12/15-LOX activation promotes local and systemic inflammation. Dobrian et al. have shown increased expression of 12/15-LOX in visceral fat of obese human patients, which correlated, with increased mRNA levels of IL-6, IL-12, IFN© and CXCL10 (279). Furthermore, it was demonstrated that 12/15-LOX deficiency protects mice from high fat diet-induced obesity and adipose tissue inflammation (233,234). 12/15-LOX products, 12(S)-HETE and 12(S)-HPETE, induce inflammation, insulin resistance, and endoplasmic reticulum stress when added to 3T3-L1 adipocytes (280). In addition, expression of various LOX isoforms were reported in human visceral adipose tissue (281). All these observations can lead to the assumption that 12/15-LOX plays an important role in obesity and obesity-induced consequences, although the underlying mechanisms remain to be explored.

8. CONCLUSIONS AND FUTURE PERSPECTIVES

12/15-LOX is expressed in various cell types and organs of the body and is implicated in a variety of diseases, including atherosclerosis, hypertension, diabetes, obesity and neurodegenerative disorders. The expression pattern of 12/15-LOX and production of its metabolites exhibit cell and tissue-specific effects and play differential roles in their pathologies. Several questions are still unanswered with respect to its differential roles in different tissue types, and more precisely about the effects of its metabolites in these tissues. Therefore, studies using cell or tissue-specific or conditional knockout mice models may allow us to identify its differential roles in various diseases. Presently, there are no specific LOX inhibitors that do not have non-specific antioxidant properties available. Therefore, further investigations are needed to develop and test specific pharmacological inhibitors for each LOX so that they can be used in the therapeutic interventions for human diseases.

ACKNOWLEDGEMENTS

The work in the authors' laboratories was supported by grants HL064165, HL074860 and EY04856 from NIH to GNR. The authors also express their sincere apology to investigators for missing to cite their work due to space limitation.

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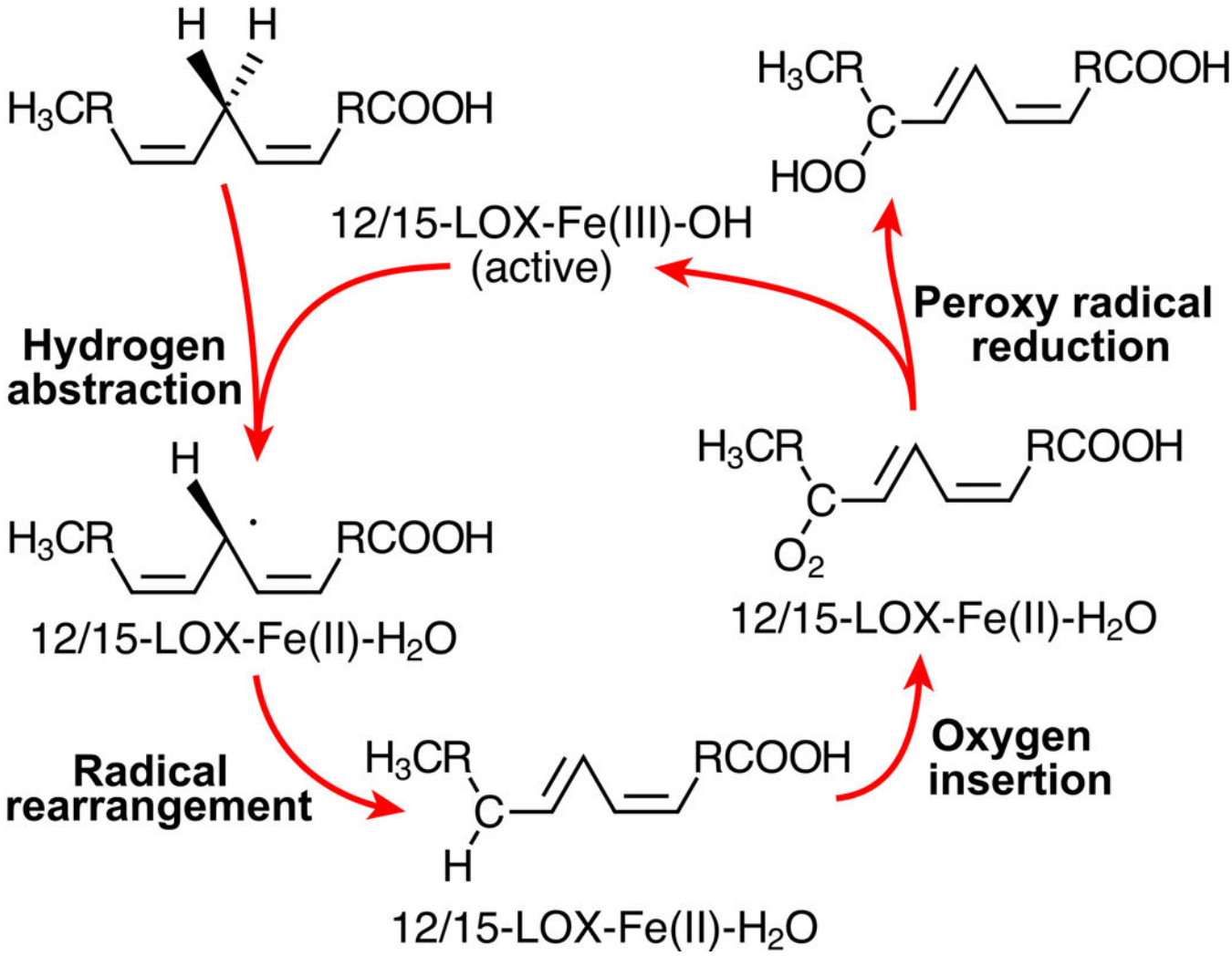


Figure 1.

A schematic diagram of 12/15-LOX catalytic reaction. 12/15-LOX catalyzes the insertion of oxygen into the hydrocarbon chain of polyunsaturated fatty acid leading to formation of fatty acid hydroperoxides in four steps. The steps are (i) hydrogen abstraction, (ii) radical rearrangement to another carbon center, (iii) oxygen insertion to the rearranged carbon radical center, and (iv) peroxy radical reduction.

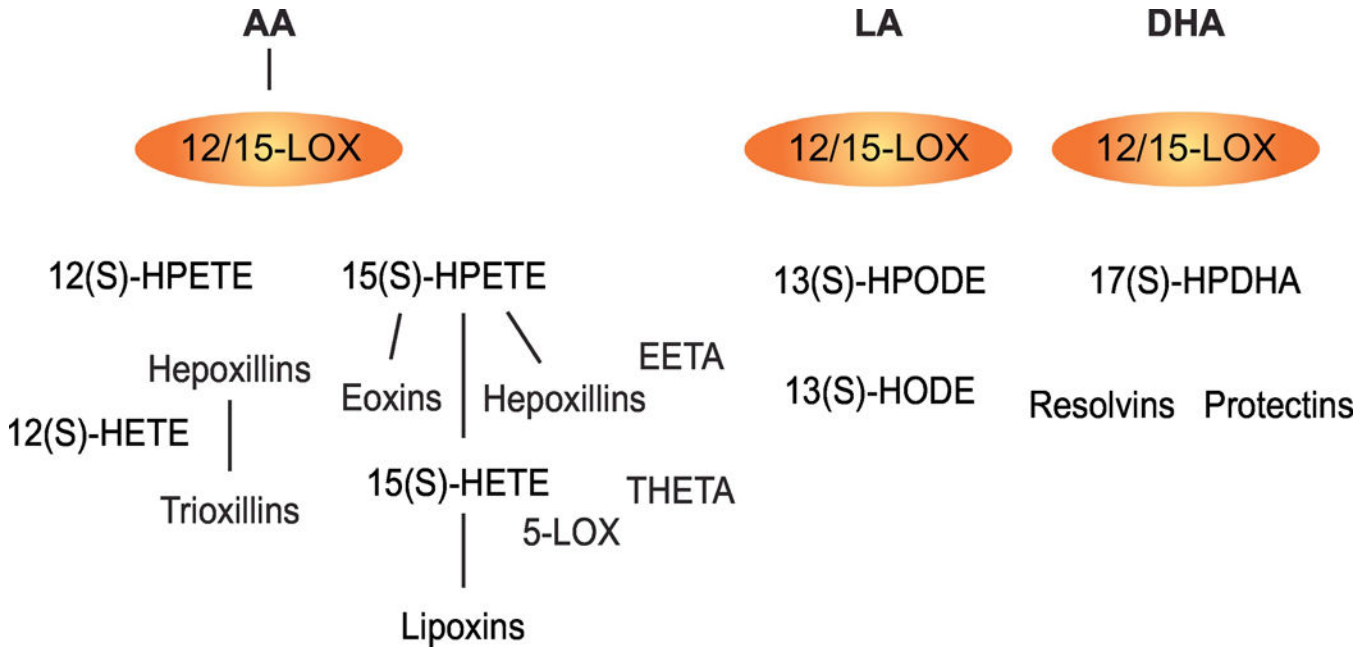


Figure 2.

Fatty acid substrates and metabolites of human 12/15-LOX. 12/15-LOX metabolizes arachidonic acid (AA) to generate 12(S)-HPETE and 15(S)-HPETE, which are further converted to their respective hydroxides, 12(S)-HETE and 15(S)-HETE, respectively. 12(S)-HPETE, 15(S)-HPETE and 15(S)-HETE can also be converted to other lipid mediators such as lipoxins, hepoxillins, trioxillins, eoxins, epoxyeicosatrienoic acid (EETA) and trihydroxyeicosatrienoic acid (THETA). 12/15-LOX metabolizes linoleic acid to generate 13(S)-hydroperoxyoctadecaenoic acid (13(S)-HPODE), which is subsequently converted to 13(S)-hydroxyoctadecaenoic acid (13(S)-HODE). Docosahexanoic acid (DHA) is metabolized by 12/15-LOX into 17(S)-hydroperoxydocosahexanoic acid (HPDHA), which is further metabolized to form resolvin Ds and protectin Ds.

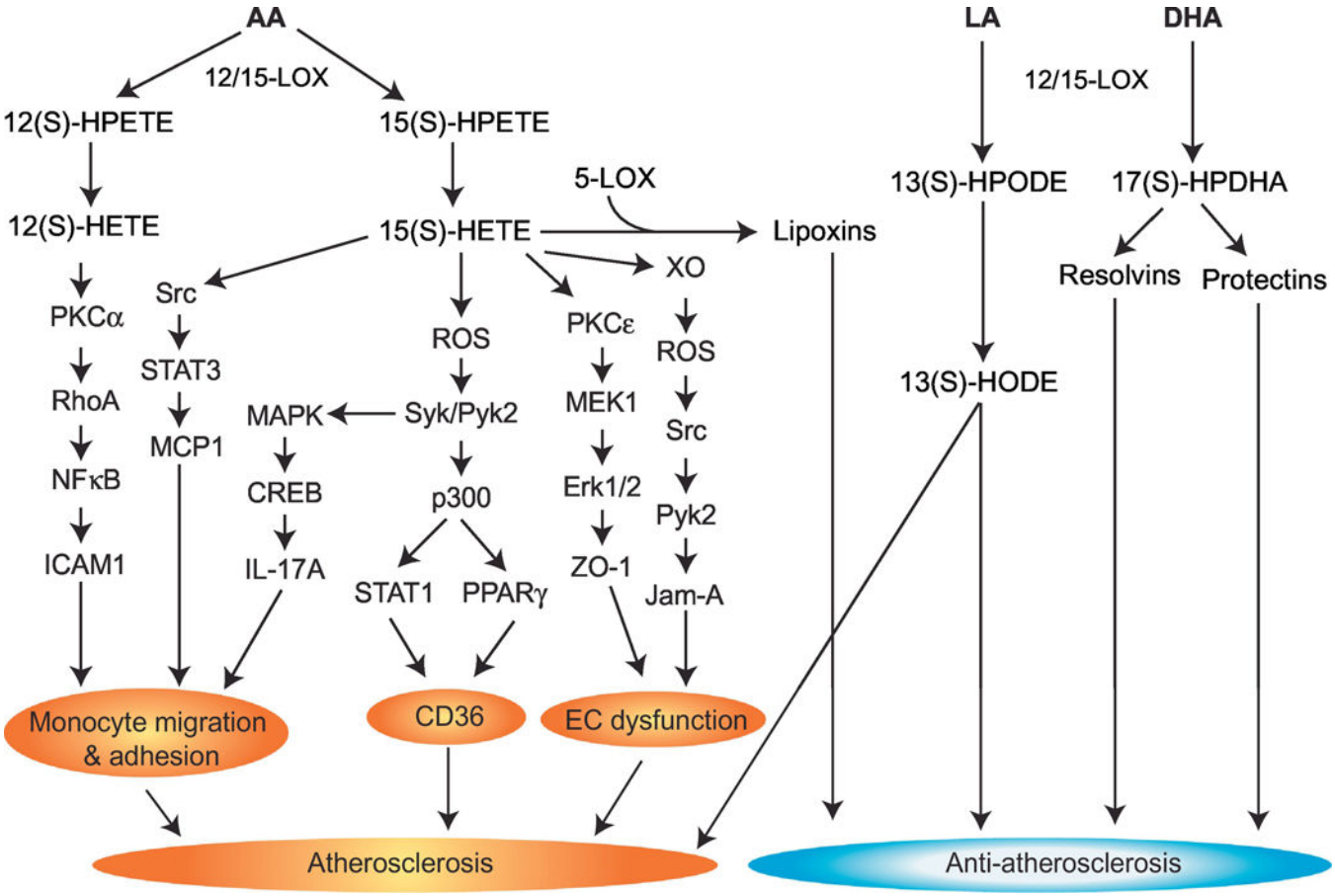


Figure 3.

Pro- and anti-atherogenic effects of various metabolites of human 12/15-LOX. 12/15-LOX metabolites of arachidonic acid (AA), 12(S)-HETE and 15(S)-HETE exert pro-atherogenic effects due to their potential role on endothelial cell (EC) dysfunction, CD36 expression, monocyte migration and foam cell formation. 13(S)-HODE, a 12/15-LOX metabolite of linoleic acid (LA) has both pro- and anti-atherogenic effects. Lipoxins, protectins and resolvins are associated with resolution of inflammation and thereby have anti-atherogenic effects.

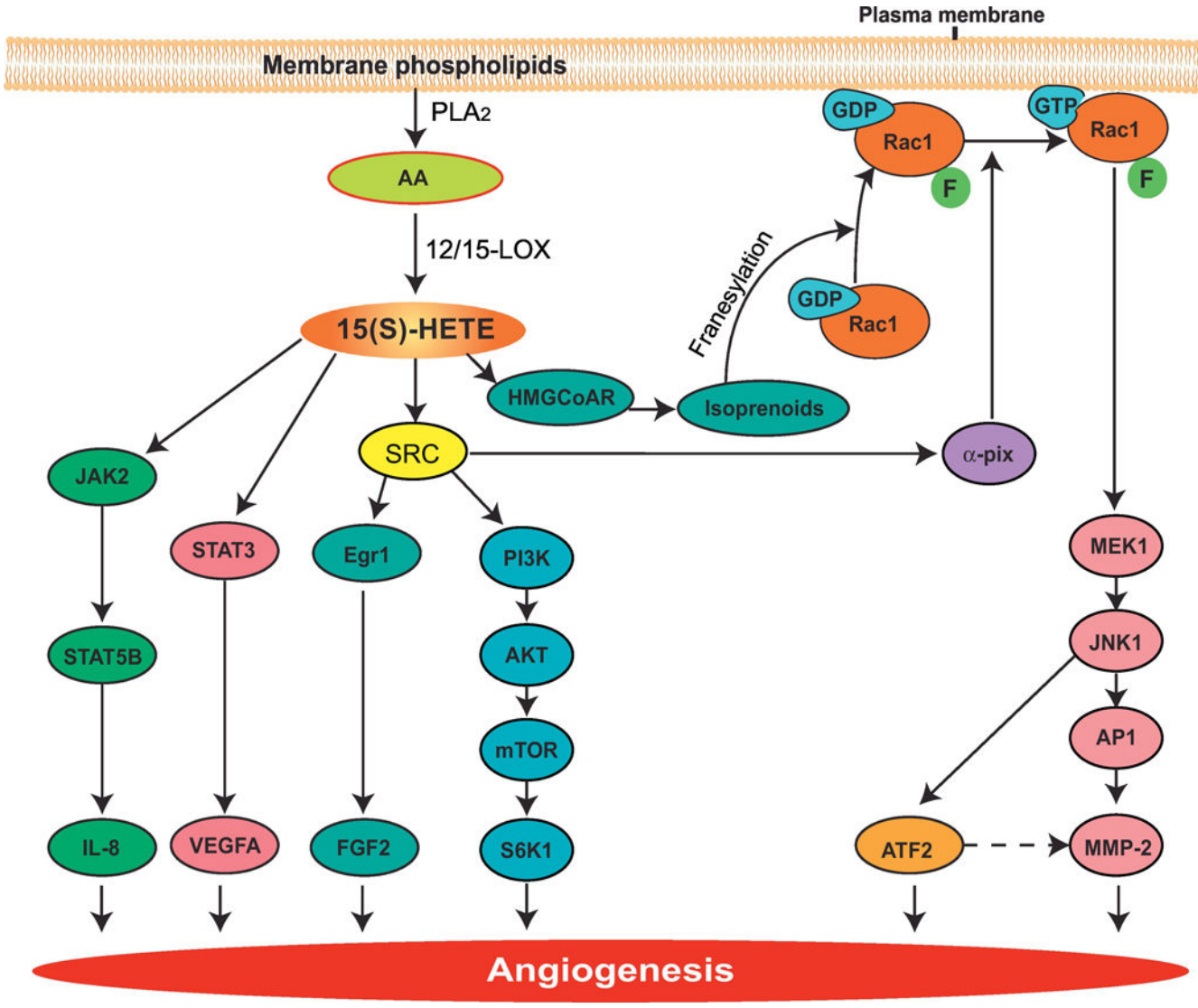


Figure 4.

A schematic diagram depicting the potential mechanisms by which 15(S)-HETE induces angiogenesis. 15(S)-HETE-induced angiogenic events appear to be preferentially mediated by Src, a non-receptor tyrosine kinase, and Rac1, a Rho GTPase. 15(S)-HETE regulates the expression of pro-angiogenic cytokines (IL-8 and VEGF) through JAK-STAT pathway in endothelial cells. 15(S)-HETE induces both physiological and pathological angiogenesis via regulating the HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase expression and matrix metalloproteinases (MMPs, particularly MMP-2) activation. The broken arrow indicates the possible mechanism by which activating transcription factor (ATF) 2 might regulate MMP-2 expression and angiogenesis.

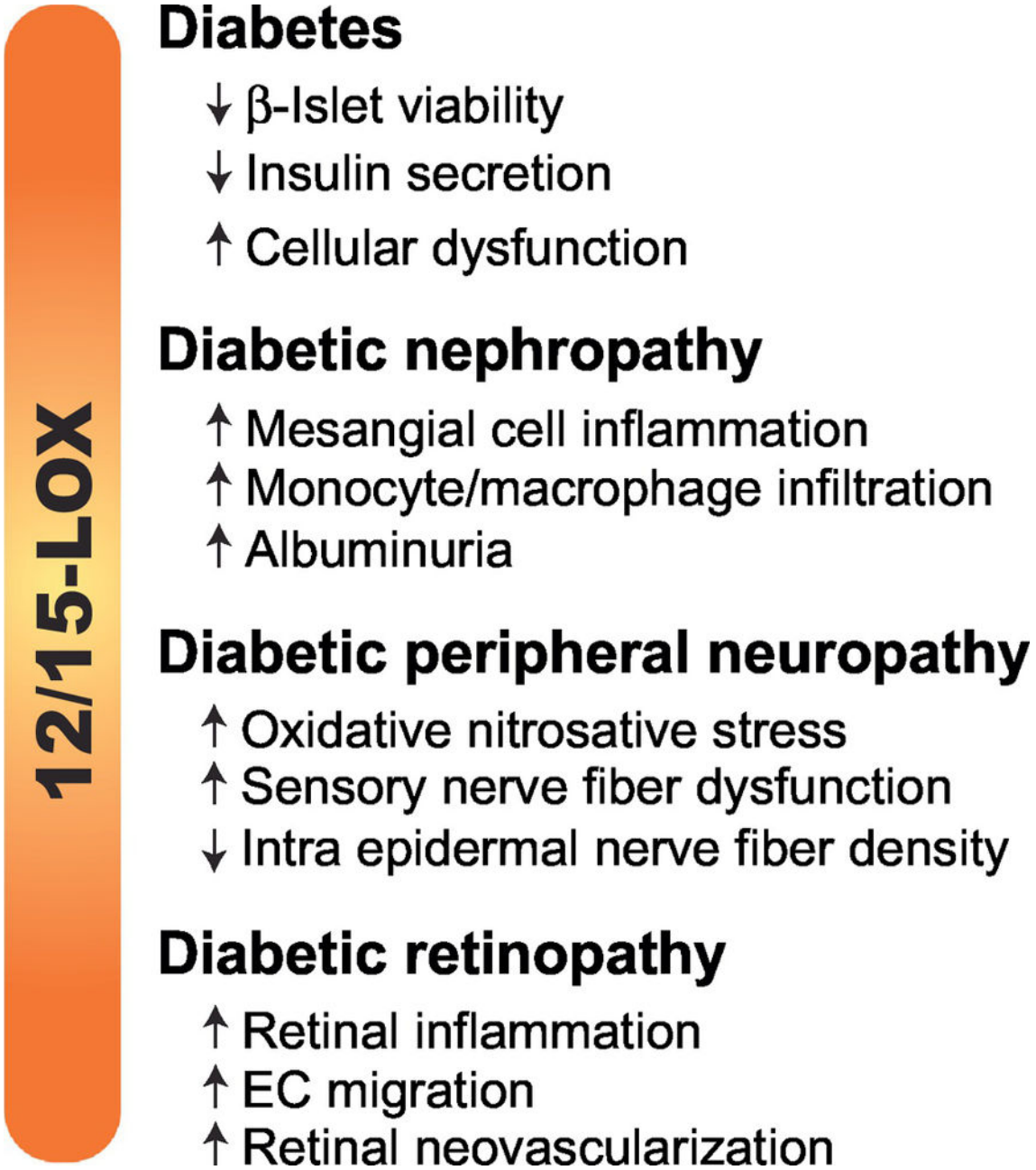


Figure 5.
The potential involvement of 12/15-LOX in the pathogenesis of diabetes and diabetes-related disorders.

Table 1

Human and murine LOX isozymes, their substartes, products and tissue distribution

	Main substrates	Main products	Tissue distribution	References
Human LOXs				
AL0X5	Arachidonic acid	5(S)-HPETE	Leukocytes, mast cells, dendritic cells and B-lymphocytes	[293]
ALOX12	Arachidonic acid	12(S)-HPETE	Platelets and leukocytes	[285,286]
ALOX15	Arachidonic acid	15(S)-HPETE 12CS1-HPETE	Eosinophils, reticulocytes and epithelial cells	[70], [282], [283]
	Linoleic acid	13(S)-HPODE		
AL0X15B	Arachidonic acid	15(S)-HPETE	Hair follicles, epidermis and prostate	[295]
	Linoleic acid	13(S)-HPODE		
ALOX12B	Arachidonic acid	12(R)-HPETE	Epidermis	[287]
	Linoleic acid	9(R)-HPODE		
AL0XE3	Arachidonic acid	12(R)-HPETE	Epidermis	[291]
	Linoleic acid	9(R)-HPODE		
Mouse LOXs				
Alox5	Arachidonic acid	5(S)-HPETE	Leukocytes, mast cells, dendritic cells and B-lymphocytes	[294]
Alox12	Arachidonic acid	12(S)-HPETE 15(S)-HPETE	Platelets and leukocytes	[292]
Alox15	Arachidonic acid	15(S)-HPETE 12(S)-HPETE	Eosinophils, reticulocytes and Epithelial cells	[159]
Alox15b	Arachidonic acid Linoleic acid	8(S)-HPETE 9(S)-HPODE	Hair follicles, epidermis and prostate	[284]
Alox12a	Arachidonic acid Linoleic acid	12(R)-HPETE 9(R)-HPODE	Epidermis	[288]
Alox3	Arachidonic acid Linoleic acid	12(R)-HPETE 9(R)-HPODE	Epidermis	[289,290]
Alox12e	Methylated polenoic fatty acids	12(R)'HPETE Methyl ester	Epidermis	[10]

Table 2

12/15-LOX metabolites and their receptors

12/15-LOX products	Receptors	References
15(S)-HPETE/15(S)-HETE	a) Leukotriene B4 receptor 2 (BLT2)	[296]
	b) PPARγ	[297]
12(S)-HPETE/12(S)-HETE	a) GPR31	[298]
	b) Leukotriene B4 receptor 2 (BLT2)	[296]
	c) Thromboxane receptor	[299]
13(S)-HODE	a) PPARγ	[300]
	b) PPARβ	[301]
	c) TRPV1	[302]
Hepoxillins	a) TRPV1 and TRPA1	[303]
	b) Thromboxane receptor α-isoform	[304]
Lipoxins	a) FPR2/ALX	[305]
	b) Estrogen receptor α	[306]
	c) Cysteinyl leukotriene receptor 1	[307]
	d) Arylhydrocarbon receptor (AHR)	[308]
Resolvin D1	a) GPR32	[309]
	b) FPR2/ALX	[309]
Resolvin D2	a) GPR18	[310]
Resolvin El	a) Chemokine like receptor 1 (CMKLR1)	[311]
Protec tin D1	a) Protectin D1 receptor	[312]

Table 3

The main substrates and products of 12/15-LOX with their biological activities

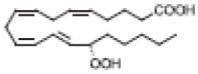
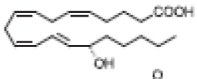
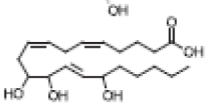
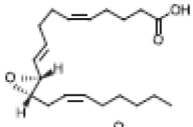
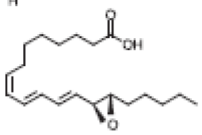
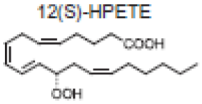
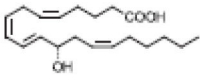
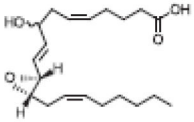
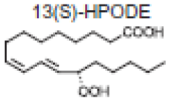
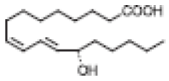
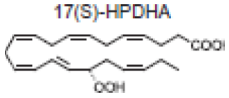
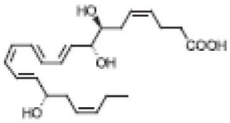
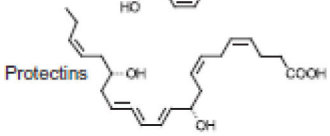
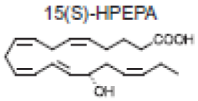
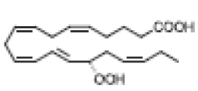
Substrates	Immediate products	End products	Biological activities
Arachidonic acid	15(S)-HPETE 	15(S)-HETE 	include immunosuppression, regulate T lymphocyte function, stimulate EC migration and neovascularization
		THETA 	stimulate vasodialation; regulate inflammatory response and insulin secretion
		Hepoxillins 	exert proinflammatory actions and cause severe asthama & allergic reactions
		Eoxins 	
	12(S)-HPETE 	12(S)-HETE 	stimulates SMC, EC and leuckocyte migration
		Trioxillins 	regulate vasodialation, pain perception, insulin secretion & reduce oxidative stress
Linoleic acid	13(S)-HPODE 	13(S)-HODE 	stimulates monocyte maturation, lipid metabolism and neuron activation
DHA	17(S)-HPDHA 	Resolvins 	resolve inflammation
		Protectins 	exert anti-inflammatory, anti-apoptotic & neuroprotective effects
EPA	15(S)-HPEPA 	15(S)-HEPA 	exerts anti-inflammatory & pro-resolving effects

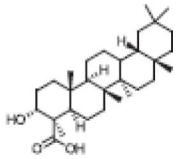
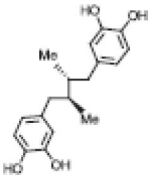
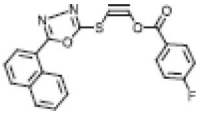
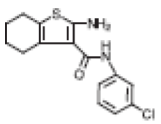
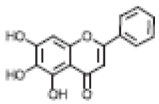
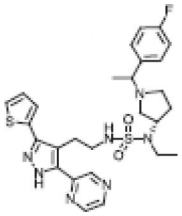
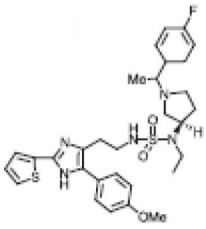
Table 4

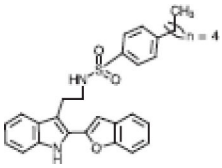
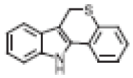
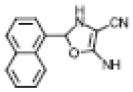
The pro- and anti-inflammatory effects of 12/15-LOX

Pro-inflammatory effects	Anti-inflammatory effects
Induces MCP1 expression and promotes infiltration of macrophages [50].	Prevent leukocyte migration and cytokine secretion [313].
Increases expression of pro-inflammatory eoxins [61].	Inhibit pro-inflammatory cytokine production by macrophages [77].
Promotes severity of asthama [62,63].	12/15-LOX deficiency leads to impaired wound healing response and increased fibrosis [78,79].
Potentiate airway allergic inflammation [60].	
Induces inflammatory cytokine generation [52].	12/15-LOX deletion results in exacerbated inflammatory joint distinction [75].
Induces plasma exudation in rabbits [53].	
Mediate LPS induced pulmonary inflammation and injury [55].	Prevents inflammation in ischemic brain [74].
12/15-LOX deficiency protects mice from DSS-colitis [65].	Promotes anti-inflammatory macrophage phenotype [12,68].

Table 5

The potentially known 12/15-LOX inhibitors [314–323].

12/15-LOX Inhibitors	Structure	IC50	Species	References
alpha-Boswellic acis		1μM	human	314
nor-dihydroguaiaretic acid (NDGA)		110 nM	human	315
MLO94		10 nM	human	316
LOXBlock-1		300 nM	human	317
Baicalein		1.6 μM	human	318
15i		3.1 nM	rabbit	319
21n		75 nM	rabbit	320

12/15-LOX Inhibitors	Structure	IC50	Species	References
371		21 nM	rabbit	321
PD146176		0.54 μM	human	322
ML351		200 nM	human	323