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REVIEW ARTICLE

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Emerging cellular functions of the lipid metabolizing enzyme 15-Lipoxygenase-1

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Abstract

The oxygenation of polyunsaturated fatty acids such as arachidonic and linoleic acid through lipoxygenases (LOXs) and cyclooxygenases (COXs) leads to the production of bioactive lipids that are important both in the induction of acute inflammation and its resolution. Amongst the several isoforms of LOX that are expressed in mammals, 15-LOX-1 was shown to be important both in the context of inflammation, being expressed in cells of the immune system, and in epithelial cells where the enzyme has been shown to crosstalk with a number of important signalling pathways. This review looks into the latest developments in understanding the role of 15-LOX-1 in different disease states with emphasis on the emerging role of the enzyme in the tumour microenvironment as well as a newly re-discovered form of cell death called ferroptosis. We also discuss future perspectives on the feasibility of use of this protein as a target for therapeutic interventions.

1 | INTRODUCTION

The polyunsaturated fatty acids (PUFAs) arachidonic acid (AA) and linoleic acid (LA) and the enzymes that metabolize these PUFAs have emerged to be essential regulators of crucial cellular processes in the context of cancer and inflammation. AA is a 20-carbon fatty acid that is released from phospholipids of the nuclear membrane with the activity of phospholipase A2 (PLA_2), which is further metabolized by cyclooxygenases (COXs) or lipoxygenases (LOXs).[1] Alternatively, the essential fatty acid LA can be processed in most mammalian cells to AA.[2] When AA is metabolized by COX-1 or COX-2, it gives rise to eicosanoids such as prostaglandins. COX-1 is expressed constitutively for many essential functions, while COX-2 expression is inducible and the produced prostaglandins are essential for pain and inflammation. On the other hand, metabolism of AA through the LOX pathway leads to the production of leukotrienes (LTs), which can act as inflammatory mediators, or in a temporal manner be further metabolized into precursors such as lipoxins (Lxs) that are essential for the resolution of inflammation.[1] Metabolism of other PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) through LOXs result in the production of a series of compounds known as resolvins (Rvs) and protectins that have roles in the resolution of inflammation.[3,4]

Lipoxygenases can be classified into several categories based on the position of the carbon on AA that is oxygenated. Human LOX enzymes include 5-LOX, 12-LOX and 15-LOX. Human *ALOX15* was initially named arachidonate 15-lipoxygenase (ALOX15) or 15-lipoxygenase (15-LOX). Subsequent studies uncovered a second human enzyme with 15-lipoxygenase activity. Therefore, the product of human *ALOX15* gene is now referred to as 15-LOX-1, and the second discovered human 15-lipoxygenase, a product of the *ALOX15B* gene, is called 15-LOX-2.[5,6] 15-LOX-1 catalyses its preferred substrate LA to 13-hydroxyoctadecadienoic acid (13-HODE); 15-LOX-2 preferentially acts on AA to produce 15-hydroxy-5Z,8Z,11Z,13E-eicosatetraenoic acid (15-HETE).[7] The production of 13-HODE or 15-HETE may have very different outcomes in a cell in terms of neoplastic transformation[8] (Figure 1; described in detail later).

15-LOX-1 is primarily expressed in reticulocytes and macrophages.[9] The *ALOX15* gene is located on chromosome 17, p13.3 locus, and has 14 exons (GenBank: NC_000017). It shares 40% identity with 15-LOX-2.[10] The 15-LOX-1 protein has a C-terminal domain that has been shown to be important for catalytic activity and an N-terminal β-barrel domain that resembles the C-terminal β-barrel domain of the human pancreatic lipase.[11] The enzyme is located in the cytosol, but may be associated with organelles such as the endoplasmic reticulum and mitochondrial membranes.[12] Herein, we summarize available data on the activity, transcriptional regulation and inflammatory functions

The authors Melis Çolakoğlu and Sinem Tunçer have contributed equally to this study.

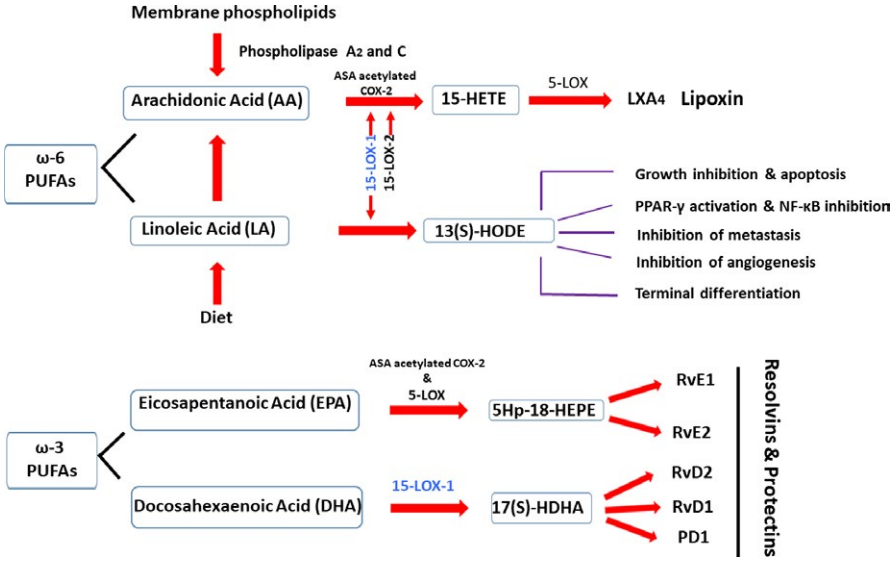

FIGURE 1 Metabolism of ω-3 & ω-6 PUFAs by 15-LOX-1 results in the production of bioactive lipids with varying functions in inflammation and cancer. The ω-6 polyunsaturated fatty acid (PUFAs) arachidonic acid (AA) is obtained from membrane phospholipids and converted to 15-HETE as a minor product of 15-LOX-1 and a major product of 15-LOX-2. 15-HETE can be further converted to Lipoxins in the presence of 5-LOX. The PUFA LA, an essential fatty acid, is oxygenated to 13(S)-HODE by 15-LOX-1. Both of the bioactive lipids have important roles in cancer. The ω-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), also known as fish oils, are oxygenated by aspirin acetylated COX-2, 15-LOX-1 and 5-LOX in a transcellular and temporal manner producing the E- and D-series of Resolvins and Protectins. These autacoids, along with Lipoxins, are generated during the resolution phase of inflammation

of 15-LOX-1 and discuss the newly described roles of 15-LOX-1 and its related pathways in the context of inflammation and cancer, with particular emphasis on the tumour microenvironment (TME).

2 | ENZYMATIC ACTIVITY OF 15-LOX-1

In addition to free fatty acids such as AA and LA, 15-LOX-1 can oxygenate a broad range of substrates that include esterified forms of naturally occurring polyenoic fatty acids, even when they are bound to biomembranes or lipoproteins.[12] The enzyme has been shown to bind to biomembranes through its N-terminal domain[12] and is therefore thought to be in close proximity for direct oxygenation of complex lipids. Alternatively, it may oxygenate free fatty acids; the products, namely 15-HETE and 13-HODE, are more polar and may be incorporated into the membrane phospholipids.[13] Additionally, 15-LOX-1 metabolites have been shown to activate NADPH oxidases leading to the production of reactive oxygen species (ROS),[14] which in turn may also oxygenate membrane lipids. It is therefore plausible that 15-LOX-1 itself, or its oxygenation products may cause alterations in the structure of biomembranes and thereby alterations in cellular functions.

3 | REGULATION OF 15-LOX-1 EXPRESSION

Regulation of *ALOX15* expression is complex and involves multiple mechanisms including transcriptional and epigenetic regulation.

3.1 | Transcriptional regulation

The expression of 15-LOX-1 in various cell types (both epithelial and stromal) was shown to be up-regulated when the cells were treated with the anti-inflammatory T-helper subset 2 (TH-2) cytokines IL-4 or IL-13.[15,16] An up-regulation of 15-LOX-1 expression was also observed during differentiation of $CD34^+$ hematopoietic progenitor cells to dendritic cells in the presence IL-4 and GM-CSF.[17] In human macrophages, which appear to constitutively express 15-LOX-1 at low levels, IL-13 induced 15-LOX-1 mRNA and protein synthesis leading to enhanced production of 15-HETE.[18]

Stimulation of 15-LOX-1 expression by IL-4 and IL-13 involves the transcription factor STAT-6[15] (Figure 2A). In human monocytes, induction of JAK2 and TYK2 tyrosine kinases by IL-13 induced 15-LOX expression, through STAT-6 dimerization and nuclear import.[19] However, IFN-γ, a product of TH-1 lymphocytes, was observed to inhibit *ALOX15* gene expression induced by IL-13 in monocytes.[20] IL-4 mediated induction of 15-LOX-1 in A549 cells[21,22] was shown to be through the up-regulation of the histone acetyltransferase activity of the Creb-binding protein/p300 (CBP/p300), which can acetylate both nuclear histones and STAT-6 in lung carcinoma cells (Figure 2B). In the same study it was suggested that IL-4 stimulation caused STAT-6 phosphorylation; and *ALOX15* expression was enhanced provided the relevant histones were acetylated and the STAT-6 binding sites became unmasked.[23] Ku autoantigen (DNA helicase) was also shown to induce 15-LOX-1 gene expression in A549 cells after treatment with IL-4 and IL-13.[24] Additionally, STAT-1 and STAT-3 phosphorylation through p38 MAPK activation was shown to be important for 15-LOX-1 expression in human primary monocytes after IL-13 treatment.[25]

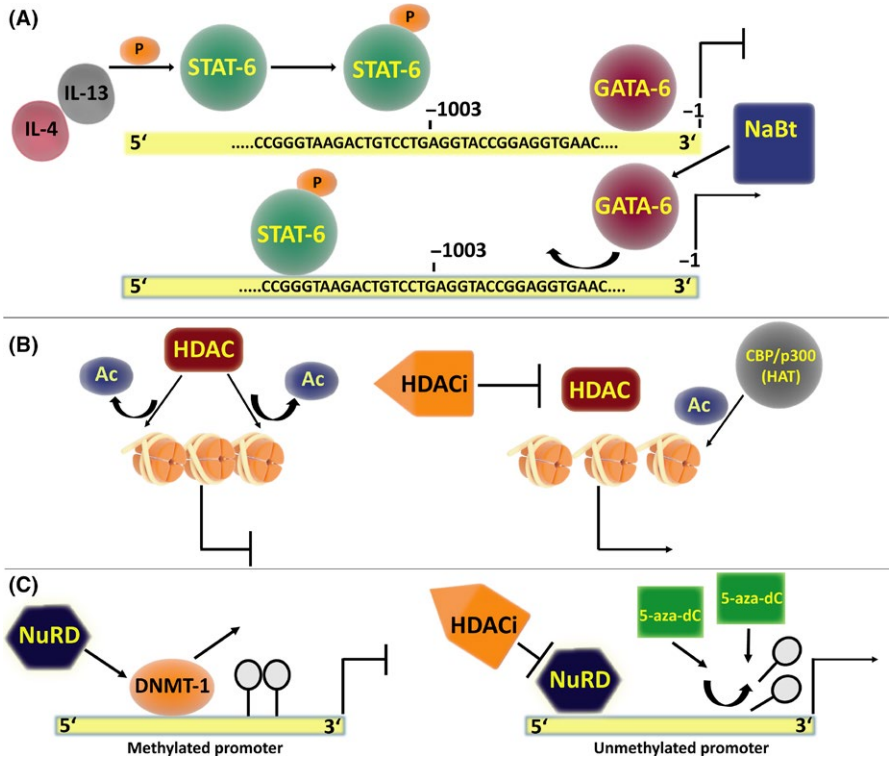

FIGURE 2 Transcriptional regulation of *ALOX15* promoter in cancer. A, IL-4 and IL-13, mediated phosphorylation of STAT-6 protein allows its entry to the nucleus to act as a transcription factor for 15-LOX- 1. GATA-6 acts as a repressor of *ALOX15* expression; treatment with the HDACi sodium butyrate has been shown to inhibit the binding of GATA-6 to the promoter, thus enhancing the expression of 15-LOX-1. B, Continued acetylation of histones by histone deacetylase inhibitors (HDACi) or acetylation of histones with histone acetyl transferases (HATs) such as CBP/p300 prevents chromatin condensation and induce the expression of 15-LOX-1. C, Methylation of the *ALOX15* promoter is a commonly observed in colon cancer samples and cell lines where the gene is silenced. The DNA methyl transferase DNMT-1 and the chromatin remodelling complex NuRD compete for binding and repress the *ALOX15* promoter. HDACi may deactivate the NuRD complex for the re-expression of 15-LOX-1. Treatment with the DNA methyltransferase agent 5-Aza-2′-deoxycytidine(5-aza-dC) can de-methylate the promoter and enhance expression in colon cancer cells.

Wittwer et al screened the entire coding region and 2 kb from 3′UTR of *ALOX15* from 44 healthy Caucasians and reported that a single nucleotide polymorphism -292C-to-T base exchange, resulted in higher transcription of 15-LOX-1 in human macrophages by generating a novel SPI1 transcription factor binding site.[26] On the other hand, GATA-6 was shown to contribute to transcriptional suppression of 15-LOX-1 probably by preventing the binding of activator proteins. GATA-6 expression was reported to be higher in transformed colon epithelial cells than the normal epithelia.[27] Shureiqi et al have shown that in colon cancer cell lines, GATA-6 knockdown was insufficient by itself but contributed significantly to restoring 15-LOX-1 expression.[27]

3.2 | Epigenetic regulation

Chromatin structure can influence gene transcription, through post-translational modifications of histones (eg, acetylation, methylation etc.).[28] Histone remodelling appears to be an important regulatory mechanism for the near universal loss of 15-LOX-1 expression in cancer cells, particularly in colorectal cancer (CRC). Methylation of histones was also implicated in the regulation of 15-LOX-1 expression. Liu et al showed that independent of STAT-6 activation, 15-LOX-1 transcriptional up-regulation in colon cancer cells required H3K9me2 demethylation by Lysine-specific Demethylase 3A (KDM3A) and inhibition of histone H3 and H4 acetylation by depsipeptide, a selective Histone Deacetylase 1 and 2 (HDAC1 and HDAC2) inhibitor (HDACi).[29] Similarly, other nonspecific HDACi's, suberoylanilide hydroxamic acid (SAHA), sodium butyrate (NaBt) and HC toxin, were also shown to induce 15-LOX-1 transcription and protein expression in colon cancer cells.[30-32] In line with this, the nucleosome remodelling and deacetylase (NuRD) complex, consisting of core proteins HDAC1, HDAC2, Mi2, MTA1/2/3 and others, was shown to suppress 15-LOX-1 expression in CRC.[33] HDACi can inhibit the core HDAC components of this complex, which in turn may contribute to the re-activation of 15-LOX-1 transcription[33] (Figure 2C).

Methylation status of *ALOX15* promoter was also studied in a broad range of cell types. *ALOX15* was shown to be methylated in healthy human primary monocytes and T lymphocytes, lymphoma, lung, epidermoid and cervical cancer cell lines in vitro, and the methylation was associated with the transcriptional repression of 15-LOX-1. Methylation of the 15-LOX-1 promoter was reported in CRC cell lines as well as in 18 of 50 CRC patients, while promoter

methylation was not observed in the colonic mucosa of the control group with no history of CRC or polyps. This process was proposed to also be responsible for the loss of expression of 15-LOX-1 in CRC.[34] In L-428 lymphoma cells treated with the DNA methyltransferase (DNMT) inhibitor 5-aza-dC, IL-4 enhanced mRNA expression of 15-LOX-1, providing direct evidence that demethylation of the 15-LOX-1 promoter was required for IL4-induced 15-LOX-1 expression. Similar results were obtained with TSA treated L-428 cells that were pre-incubated with 5-aza-dC. Although a robust increase in the mRNA transcript of 15-LOX-1 was obtained in these cells, 15-LOX-1 protein expression was not detected, indicating that together with transcriptional suppression mechanisms, post-transcriptional and/or post-translational mechanisms can contribute to the regulation of 15-LOX-1 expression.[35]

Interestingly, the binding (rather than activity) of the enzyme DNA methyltransferase-1 (DNMT-1) to the promoter of 15-LOX-1 was found to directly suppress its transcription. Dissociation of DNMT-1 from the promoter was necessary for the reactivation of transcription in the presence of the HDACi SAHA. Interestingly, Kamitani et al did not find any effect of 5-aza-dC treatment on 15-LOX-1 expression,[31] which is compatible with the findings of Zuo et al who showed that 15-LOX-1 promoter DNA methylation was not correlated with 15-LOX-1 mRNA levels in colon cancer, and that promoter demethylation failed to reactivate 15-LOX-1 expression in vitro.[34] It was thus proposed that DNA methylation was not a primary event in the suppression of the gene. DNMT1, on the other hand, appeared to play an important role, as it could bind to the same region on the promoter where HDAC1 and HDAC2 of the NuRD complex can bind to; therefore, the occupation of this region by either DNMT1 or the members of the NuRD complex was reported to be crucial in the transcriptional fate of 15-LOX-1 in colon cancer cells.[34,35]

Expression of the mutant form of the tumour suppressor protein p53 was shown to up-regulate the human 15-LOX promoter activity in a mouse embryo fibroblast cell line, whereas it markedly inhibited mouse 12/15-LOX expression.[36] Although these results are important to indicate the divergence of these the human and mouse enzymes at the level of transcriptional regulation, further data are needed to understand whether a similar regulation may occur in human cancer cells, in tumours harbouring different types of p53 mutations, or in tumours where p53 is lost. Additionally, since human *ALOX15* is present on chromosome 17p13.3 in close proximity to *TP53*,[36] the co-regulation of these two genes at the level of transcription needs to be analysed in terms of the dynamics of the chromatin structure.

4 | 15-LOX-1 IN CARCINOGENESIS

The expression of 15-LOX-1 is lower in diverse cancer types compared to the normal cells. In a screen of 128 randomly collected cancer cell lines representing more than 20 types of human cancers, Moussalli et al showed that 15-LOX-1 mRNA expression was considerably lower in cancer cells compared to terminally differentiated cells.[37] In nonsmall cell lung cancer (NSCLC) patients, decreased expressions of 15-LOX-1 and 15-LOX-2 were shown to reduce the production of PUFA oxygenation products, which in turn led to decreased activity of peroxisome proliferator-activated receptor-gamma (PPAR-γ),[38] resulting in loss of apoptosis and enhanced cell proliferation.[39] In breast carcinoma, 15-LOX-1 and 15-LOX-2 staining was shown to be low in metastatic patients specimens[40] and in pancreatic cancer, low 15-LOX-1 expression or complete loss of expression was observed.[41] Examination of normal human bladder and bladder tumour specimens indicated a statistically significant decrease in 15-LOX-1 expression in stage T3/T4 bladder tumours compared with normal tissues.[42] Adenoviral transfection of 15-LOX-1 in a syngeneic rat model of malignant glioma led to the induction of apoptosis through caspase-3 activation, reduction in tumour volume and enhanced survival, significantly.[43]

The effect of 15-LOX-1 on CRC has been investigated extensively with a consistent loss in expression and activity of the protein reported. In a cohort of primary colorectal carcinoma, decreased 15-LOX-1 expression as well as 13-HODE levels were reported in human colorectal adenomas and carcinomas compared to the normal mucosa.[44,45] Treatment of colon carcinoma cell line Caco-2 with 13-HODE resulted in decreased cell proliferation.[46] In the same study, it was shown that in adenoma tissues 15-LOX-1 expression was spread throughout the sample with a lower intensity of staining in the neoplastic epithelium and a higher intensity of staining in the inflammatory areas while in normal controls the expression was mostly restricted to the colonic mucosal epithelium.[46] Based on this finding, it might be possible to argue that 15-LOX-1 expression must be maintained at a high concentration in a confined area for its biological effects, and that in the case of neoplastic transformation, colon cells evade 15-LOX-1-mediated apoptosis through the dispersion of the expression pattern. Furthermore, tumours derived from the colon cancer cell line HCT-116 that ectopically expressed 15-LOX-1 were smaller than the tumours derived from empty vector-expressing HCT-116 cells in athymic nude mice.[46] Re-expression of 15-LOX-1 by adenoviral transfection to HT-29 and LoVo CRC cells inhibited growth of cancer cells in xenografts and down-regulated important anti-apoptotic markers like XIAP and Bcl-xL, suggesting pro-apoptotic properties of 15-LOX-1.[47] Treatment of RKO and HT-29 cells with sulindac and NS-39 led to increased 15-LOX-1 expression and subsequent 13-HODE production, cell growth inhibition and increased apoptosis.[48] In the same study, the effects of the NSAID treatments became unobservable when 15-LOX-1 was inhibited with caffeic acid.[48] In addition, exogenous addition of 13-HODE to these cells led to growth inhibition and apoptosis.[48] Treatment with celecoxib, another NSAID that selectively inhibits COX-2, resulted in increased 15-LOX-1 expression and induction of apoptosis, suggesting a therapeutic role of celecoxib in CRC.[44] Interestingly, a negative correlation between the expression and activity of 15-LOX-1 and COX-2 has been reported in colonic neoplasia indicating an alteration in the species of bioactive lipids

being produced in the malignant tissues from the pro-apoptoic molecules to the more mitogenic prostaglandins.[49]

On the other hand, some studies suggest a pro-carcinogenic role of 15-LOX-1 signalling. 15-LOX-1 expression was shown to be dramatically high in prostate cancer tissues, primarily in high-grade tumours, as compared to normal tissue samples.[2] Transgenic mouse models (human fifteen lipoxygenase-1 in mouse prostate, FliMP), as well as cell line studies suggested enhanced proliferation in the presence of 15-LOX-1.[50,51] These studies, however, have been refuted recently. Bioactive lipids produced from the metabolism of DHA by 15-LOX-1 in prostate cancer cells were shown to reduce cell proliferation by activating PPAR-γ signalling and induction of apoptosis.[52] Moreover, the same lipid products were shown to be important for the activation of syndecan-1 (SDC-1), a protein that is important in cell to matrix interactions, cellular proliferation and migration as well as caspase-3 activity.[52] Zhong et al have shown that 15-LOX-1 expression in prostate cancer cells led to the ubiquitin mediated degradation of Hypoxia Inducible Factor 1α (HIF-1α), a transcription factor that is essential for neoangiogenesis.[53] 15-LOX-1 was shown to be expressed more in hepatocellular cancer cell lines compared to normal hepatic cells with a further exacerbation of expression under hypoxic conditions in cancer cells. Again, in this case the composition of the bioactive lipids produced was of importance since the production of 15-HETE, but not 13-HODE, led to the activation of phosphoinositide-3 kinase (PI3K)/Akt/Heat Shock Protein 90 pathway resulting in several pro-carcinogenic changes in the cells.[54]

Ferroptosis is a newly described form of cell death that differs from traditional apoptosis and necrosis. Ferroptosis results from the accumulation iron-dependent lipid peroxides and is characterized by cell volume shrinkage and increased mitochondrial membrane density.[55] Recently, SAT1 (spermidine/spermine N^1-acetyltransferase 1), a transcriptional target of p53, was shown to induce ferroptosis via 15-LOX-1 in human nonsmall cell lung carcinoma cell line H1299. The authors claimed that SAT1 increased the expression of 15-LOX-1, and the cells treated with the 15-LOX-1 inhibitor PD146176 rescued SAT1-induced ferroptosis.[56] These results support earlier findings which state that 12/15-lipoxygenase dependent lipid peroxide signalling could activate apoptosis-inducing factor (AIF)-mediated cell death in a neuronal degeneration model.[57] Inhibition of ferroptosis in neurodegenerative diseases, characterized by accumulation of lipid hydroperoxides, offer a therapeutic alternative.[58] Similarly, the induction of ferroptosis has the potential to provide a new strategy for killing cancer cells. Future studies will establish the precise mechanisms by which 15-LOX-1 is involved in ferroptosis in different cancer models.

5 | ROLE OF 15-LOX-1 IN INFLAMMATION

Inflammation is the sum of biological processes such as swelling, redness, pain and heat. While essential during pathogenic infections, acute inflammation should be resolved when the infection is cleared out through the process of resolution. A highly regulated spatial and temporal class switching of eicosanoids occurs in inflamed tissues, starting with the production of pro-inflammatory mediators through the COX and LOX pathways followed by the production of resolution mediators such as resolvins and lipoxins.[59,60] However, overproduction of the pro-inflammatory mediators and a deficiency of resolution may lead to chronic low grade inflammation and associated diseases such as cancer.[61] 15-LOX-1 plays a dual role in inflammation as its activity generates mediators that function both in the progression and in the resolution of inflammation.

Role of 15-LOX-1 expression in colon cancer in the context of inflammation has been addressed in recent years. Since 12-HETE and 15-HETE produced by 12/15LOX (an ortholog of human 15-LOX-1) in mice may have different biological effects in cells, Shureiqi et al have generated a mouse model where human 15-LOX-1 (which oxygenates AA exclusively to 15-HETE) is overexpressed solely in the intestinal epithelium through the use of the promoter of villin, a brush border protein that is highly expressed in the colon.[62] Expression of 15-LOX-1 was shown to decrease tumour size in mice administered with the carcinogen azoxymethane (AOM). Data emerging from this model indicated a crosstalk between 15-LOX-1 expression and the inflammatory transcription factor Nuclear Factor-kappa B (NF-κB). Expression of human 15-LOX-1 resulted in a significant inhibition of the activity of NF-κB, along with lower levels of tumour necrosis factor-α (TNF-α) and its target inducible nitric oxide synthase (iNOS).[62] Mechanistically, our group has shown that the inhibition of NF-κB activity was through the phosphorylation and activation of PPAR-γ by its ligand 13-HODE in 15-LOX-1 overexpressing CRC cell lines.[38] In a colitis-associated colon cancer (CAC) model, 15-LOX-1 inhibited IL-6/STAT-3 signalling and tumourigenesis by down-regulating PPAR-δ.[63] Similarly, in a trinitrobenzenesulfonic acid-induced IBD mouse model, the administration of milk fermented by a *Lactococcus lactis* strain producing 15-LOX-1 alleviated symptoms of colitis.[64] These data collectively illustrate that chronic inflammation, a cornerstone of colon cancer may be ameliorated by the expression and activity of 15-LOX-1.

Inflammatory resolution is an active process aimed to prevent the progression from acute-resolving to persistent-chronic inflammation to inhibit further tissue damage.[65] Resolvins, protectins, lipoxins and maresins are endogenous lipid mediators that are synthesized during the resolution phase of acute inflammation.[66] The products of 15-LOX-1 pathway can induce a number of anti-inflammatory processes through the production of pro-resolving mediators. 15-LOX-1 can metabolize DHA to form D-series resolvins (RvDs) and protectins (PDs) that act as pro-resolution agents.[66] Lipoxins (LXs) are pro-resolution mediators produced by combined action of various LOXs as well as aspirin-acetylated COX-2 in a transcellular manner.[60,67] The inhibition of COX-2 with aspirin leads to the cessation of prostaglandin synthesis, but allows for the production of 15-*R*-HETE from AA and subsequently LXs.[66] 15-LOX-1 is also known to produce LXA_4 during resolution of inflammation.[60] Production of LXA_4 or 15-epi-LXA_4 from 15-HETE through the action of 15-LOX-1 or aspirin acetylated COX-2 entails an eicosanoid class switching where the state of tissue goes

from active inflammation to resolution.[68] LXA_4 was shown to inhibit inflammation caused by lipopolysaccharide (LPS)-induction in keratinocytes through the upregulation of suppressor of cytokine signalling 2 (SOCS2) and the down-regulation of TRAF6, a TNF receptor associated factor family member.[69] LXA_4 and 15-epi-LXA_4 were shown to diminish migration of neutrophils to the site of infection.[67] Moreover, it was demonstrated that PUFAs such as AA, LA and EPA could inhibit the growth of the CRC cell lines RKO and LoVo in vitro by decreasing the synthesis of leukotrienes and prostaglandins, and the expression of COX-2 while increasing the formation of LXA_4.[70] Similarly, transgenic rabbits overexpressing 15-LOX-1 in macrophages showed reduction in inflammation and associated tissue damage as well as up-regulation of LXA_4.[71] In addition, IL-13, an anti-inflammatory cytokine, was shown to up-regulate 15-LOX-1 expression in human monocytes[72] and to induce LXA_4 receptor expression in human enterocytes.[73] Among other TH-2 lymphokines, induction of 15-LOX in human peripheral blood monocytes was achieved by IL-4 stimulation, but not by IL-10. However, as a pro-inflammatory TH-1 cytokine, IFN-γ blocked IL-13-mediated induction of 15-LOX, indicating TH-lymphocyte subpopulations can modulate 15-LOX expression and inflammatory responses related to 15-LOX signalling.[20] An anti-inflammatory effect of 15-LOX-1 was also demonstrated by Munger et al by taking the advantage of in vivo gene delivery to distinguish between human and rodent 15-LOX-1 expression in rat kidney.[74] In an experimental glomerulonephritis model, glomerular leukotriene B4 (LTB_4) production was reduced while LXA_4 concentration in the urine from unilaterally 15-LOX-1 transfected animals was shown to increase, further indicating the anti-inflammatory actions of 15-LOX-1 derived eicosanoids during inflammation.[74]

On the other hand, 15-LOX-1 has also been shown to exhibit pro-inflammatory activities in various models. In dermatitis, inhibition of 15-LOX-1 resulted in impaired podosome formation in dendritic cells (DCs), immune system cells important for pro-inflammatory responses and antigen presentation, which resulted in the inhibition of their antigen uptake and migration abilities, showing the importance of 15-LOX-1 for trafficking of DCs to inflamed tissues.[75] 15-LOX-1 expression and activity was also associated to alcoholic liver disease (ALD). The initial step of ALD is the accumulation of lipid droplets in the liver. 15-LOX was found to be overexpressed in the liver of patients with ALD cirrhosis. Since lipids accumulated in the liver can stimulate inflammation, 15-LOX-1 mediated fatty acid derivatives were reported to play an important role in ALD. Furthermore, free radical peroxidation, which is elevated in ALD patients, was suggested to contribute to liver necroinflammatory injury in ALD.[76]

A number of studies have demonstrated increased expression and activity of 15-LOX-1 in lung epithelial cells as a pro-inflammatory event in the pathogenesis of asthma and other inflammatory airway diseases.[77-80] Zhao et al showed that epithelial 15-LOX-1 expression increased with increasing severity of asthma.[81] To clarify the mechanism, Liu et al overexpressed 15-LOX-1 in A549 human lung epithelial cell line and showed that 15-LOX-1 overexpression led to enhanced release of the inflammatory chemokines, and thereby increased recruitment of immature dendritic cells, mast cells and activated T cells.[80] Through 15-LOX-1, IL-13, which is up-regulated in approximately 50% of asthmatic patients, was found to induce the formation of esterified 15-HETE (15-HETE-PE) which contributed to the increase in mucin MUC5AC expression in human airway epithelial cells.[81,82] Similarly, in vitro activation of human lung macrophages by exposure to IL-4/IL-13 was associated with an increase in the expression of 15-LOX-1.[83] Using both in vivo and in vitro models of human airway epithelial cells, IL-13-induced 15-LOX-1 was shown to interact with phosphatidylethanolamine-binding protein 1 (PEBP1) to displace Raf-1 and activate MAPK/ERK pro-inflammatory signalling pathway, and induce MUC5AC expression.[84] In another study, after IL-13 treatment, binding of 15-LOX-1 with PEBP1 was shown to contribute the desensitization of β2-Adrenergic receptor (β2AR) through release of G protein receptor kinase 2 (GRK2), which may lead to loss of therapeutic effects in patients with airway diseases.[82] Therefore, 15-LOX-1 and PEBP1 interaction has been suggested as a potential target in patients with airway diseases, such as asthma, for restoring β2AR sensitization to enhance adenylate cyclase activity and cAMP synthesis, which can promote smooth muscle relaxation in airways and blood vessels as well as enhance ciliary beating and mucin clearance.[82] More recently, in silico analysis of the interaction between 15-LOX-1 and PEBP1 in humans was predicted to modify the 15-LOX-1 protein in a way that would allow the enzyme to efficiently oxygenate esterified PUFAs. In human airway epithelial cells, PEBP1 and 15-LOX-1 were shown to co-localize and enhance the formation of oxidized lipid species, which, in the absence of an efficient antioxidant system (such as GPX4) could trigger cell death via ferroptosis.[85] In a diabetic retinopathy model, a hyperglycaemia-induced reduction in 15-LOX-1 levels and downstream production of resolvin D1 (RvD1) was reported, while activation of β2AR signalling pathway rescued these decreases in 15-LOX-1 and RvD1.[86] Therefore, the biological action of 15-LOX-1 in inflammation can be different in airway epithelial cells when compared to retinal cells. It should be also noted that several mediators that elevate the inflammatory phase of inflammation can simultaneously initiate an active resolution program, which can be specific to associated pathologies,[65] with context specific molecular interactions and signalling networks.

Atherosclerosis is accepted as an inflammatory disease involving the vascular wall.[87] LOXs are involved in the pathogenesis of atherosclerosis as reviewed previously.[88,89] 15-LOX is one of the enzymes that catalyses the formation of oxidized low-density lipoprotein (ox-LDL), a major cause for atherosclerosis,[90] and polymorphisms in *ALOX15* gene was found to be associated with coronary artery disease in human.[26,91–94] ox-LDL and/or reduced cholesterol efflux leads to the deposition of esterified cholesterol in the cytoplasm of macrophages and generation of foam cells which then accumulate in the subendothelial space of the arteries and lead to atherosclerotic plaque formation.[95] In atherosclerotic lesions in humans, 15-LOX was observed to co-localize with LDL in macrophage-rich areas.[96–100] Furthermore, Makheja et al found an increased formation of 15-HETE in aortas from cholesterol fed Watanabe heritable

hyperlipidaemic (WHHL) rabbits, an indication of elevated 15-LOX activity.[101]

15-LOX-1 is also associated with endothelial cell (EC) function in the pathogenesis of atherosclerosis (for details please see Figure 3). Ox-LDL, formed through 15-LOX activity, was shown to enhance the expression of its receptor Lectin-like oxidized LDL receptor-1 (LOX-1) via the activation of NF-κB and p38 MAPK signalling pathways and ligand-receptor interaction was shown to enhance the expression of intercellular cell adhesion molecule-1 (ICAM-1) in ECs. Transient overexpression of 15-LOX in bovine aortic ECs induced the expression vascular cell adhesion molecule 1 (VCAM-1) by inflammatory stimulation.[102] Similarly, the 15-LOX-1 metabolite 15-HpETE was found to induce a subset of cell adhesion molecules (CAMs): ICAM-1, endothelial cell leukocyte adhesion molecule-1 (ELAM-1) and VCAM-1 in human umbilical vein endothelial cells (HUVECs) and increase transendothelial migration of monocyte-like cells through platelet endothelial cell adhesion molecule-1 (PECAM-1).[103] Treatment of HUVECs with Atorvastatin, a cholesterol-lowering medication, suppressed the up-regulation of the adhesion molecules whereas overexpression of 15-LOX-1 partially eliminated this effect.[104] More recently, Liu et al demonstrated that chronic hypoxia increased the expression of CAMs in pulmonary arterial endothelium cells via a positive interaction between 15-LOX/15-HETE and NF-κB,[105] underlying the influence of inflammation in the etiology of pulmonary diseases. On the other hand, the increase in expression of CAMs through 15-LOX-1-related metabolites have the potential to render endothelial cells responsive to inflammatory activation for antitumour immunity (discussed later).

Taken together, these data imply that 15-LOX-1 pathway can both stimulate inflammation or resolve inflammation. These opposed effects may depend on cell type and also substrate available in the cell at a specific time. Therefore, re-modelling of cellular characteristics by 15-LOX-1 action may modulate inflammatory cell actions in a context-dependent manner.

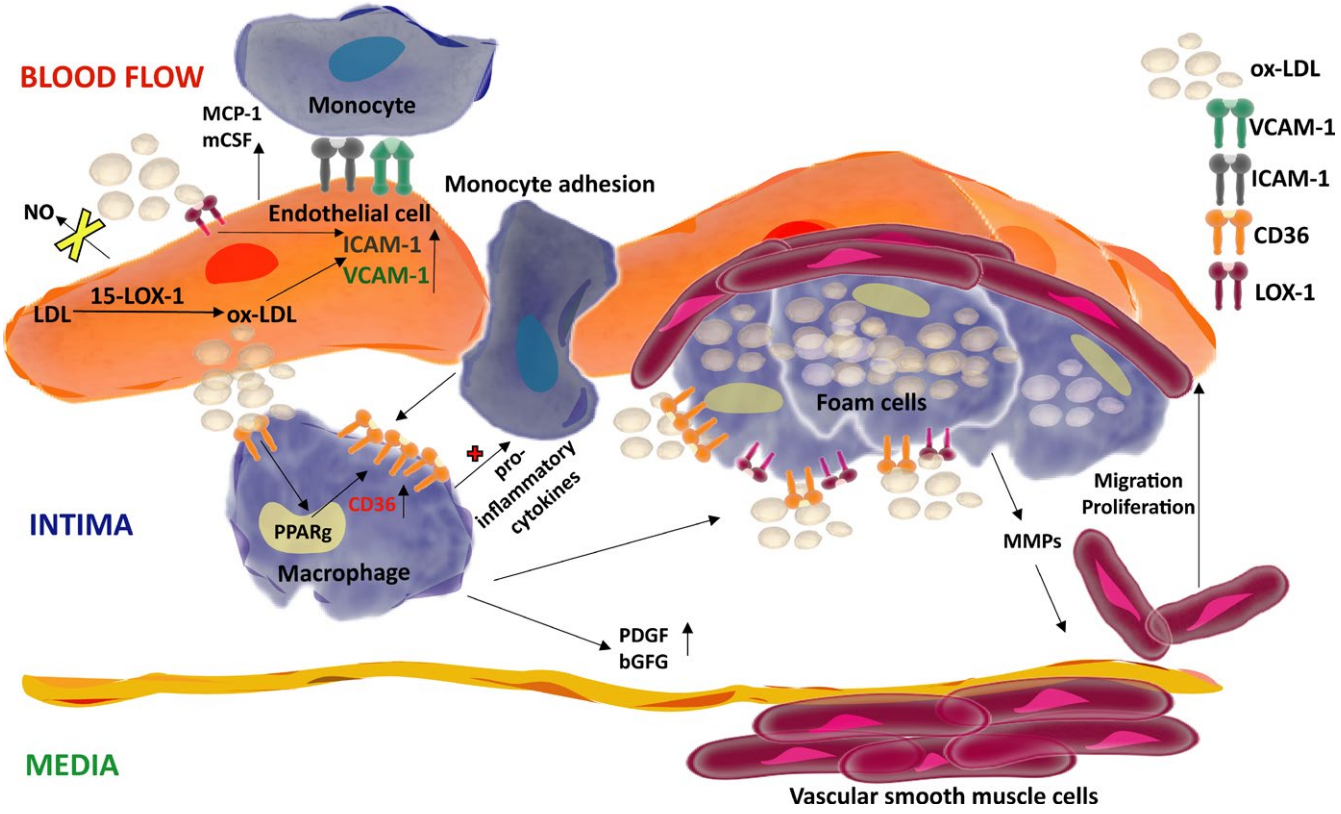

FIGURE 3 Involvement of 15-LOX-1 in the formation of atherosclerotic lesions. Formation of atherosclerotic lesions represents a series of highly dynamic events[145] initiated by endothelial dysfunction, generally accompanied by a loss of production of nitric oxide (NO). Ox-LDL generated from LDL by 15-LOX-1 activity in endothelial cells (ECs) induces the expression of cell surface adhesion molecules ICAM-1 and VCAM-1, enhancing the adhesive properties of endothelium. At early stages of plaque formation, expression of the major Ox-LDL receptor, Lectin-like oxidized LDL receptor-1 (LOX-1), increases in ECs. Moreover, Ox-LDL stimulates ECs to secrete cytokines that promote the recruitment of monocytes from blood flow into the endothelial wall (intima), and differentiate into macrophages. These macrophages express several scavenger receptors such as cluster of differentiation 36 (CD36) and LOX-1. Internalized Ox-LDL may enhance CD36 expression (via PPARγ) which in turn facilitates the internalization of more Ox-LDL, forming foam cells. ECs and macrophages also enhance platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) expression and secretion which induce vascular smooth muscle cell (VSMC) proliferation. Foam cells secrete matrix metallopeptidases (MMPs) that trigger VSMCs migration from the media into the intima via the degradation of the extracellular matrix (ECM). Later in the process, VSMCs can produce extracellular matrix factors, including interstitial collagen and elastin, and form a fibrous cap that covers the plaque, which are not shown here

6 | 15-LOX-1 IN THE TUMOUR MICROENVIRONMENT

The tumour microenvironment (TME) consists of a variety of stromal cells, including noncancerous immune cells, within the extracellular matrix (ECM) that provides for sustained growth, angiogenesis, invasion and metastasis of the tumour cells.[106] Infiltration of immune cells in the TME may be a double-edged sword. Thus, while the activation of pro-inflammatory transcription factors such as NF-κB and STAT-3 and their transcriptional targets IL-6 and TNFα are known to enhance proliferation and tumour progression,[107] immunogenic tumour cells can enhance the infiltration of $CD8^+$ T cells and Natural Killer (NK) cells, which in turn have the potential to restrict tumour growth.[108] The TME is generally tumour suppressive, with recruitment of cells such as tumour associated macrophages, myeloid derived suppressor cells (MDSCs) and regulatory T cells and the exclusion of inflammatory TH1 type cells.[109] As discussed in the previous section, 15-LOX-1 appears to play an important role in inflammation and its resolution through metabolism of the PUFAs: AA, LA, DHA and EPA. Since both epithelial and immune cells (such as macrophages) are known to express 15-LOX-1, it is likely that the composition of bioactive lipids in the TME may guide tumour progression. Although most of the studies examining the role of 15-LOX-1 in cancer have focused on expression in the epithelial cells, emerging data indicate that both epithelial and stromal derived bioactive lipids can influence the recruitment of different cell types to the TME.

6.1 | Modulation of cellular motility in the microenvironment

Metastasis is a complex process that requires cancer cells to undergo epithelial to mesenchymal transformation, detach from the resident tumour, migrate through the blood vessels to a secondary tumour site where the cells extravasate into the tissue where the cells undergo transformation to a more epithelial phenotype and promote the secondary tumour formation.[110] The TME, particularly the composition of ECM, is a significant determinant of whether a tumour can successfully metastasize to distant organs.[111] Recent data indicate that 15-LOX-1 may have an antimetastatic role, although the detailed mechanisms and specific interactions with the TME need to be elucidated.

We have shown that 15-LOX-1 re-expression in the colon cancer cell lines HCT-116 and HT-29 can enhance adhesion of cells to fibronectin, reduce cellular motility, wound healing, migration and invasion in vitro[7] through the reduced expression of MTA-1 (Metastasis-associated protein 1), a master regulator of metastasis in many tumours including CRC.[112,113] Functionally, the reduced motility seen in CRC cell lines overexpressing 15-LOX-1 was rescued when MTA-1 was overexpressed.[113] Other studies have indicated that the mechanism behind reduced motility in CRC cell lines expressing 15-LOX-1 could also be attributed to a loss of VEGF expression and secretion.[114]

Data on the role of 15-LOX-1 expression of the TME in metastatic spread is relatively limited. Activation of PPAR-γ by 13-HODE was shown to inhibit metastasis to the peritoneal cavity in an in vivo mouse gastrointestinal peritoneal metastasis model and reduced motility in human colon and gastric cancer cell lines.[115] A transgenic mouse model that over-expressed 15-LOX-1 in endothelial cells under the control of the murine preproendothelin-1 promoter showed reduced tumour metastasis in both mammary and Lewis lung cancer models.[116] The same study also reported decreased expression of EGF and increased expression of apoptosis marker Bax indicating an overall tumour suppressive effect.[116] Future studies are necessary to tease out the delicate balance between different 15-LOX-1 derived bioactive lipids in the TME and their role in epithelial-stromal cell interactions.

6.2 | Modulation of vasculature in the microenvironment

The vasculature plays a crucial role in determining the composition of the TME. Tumour associated vasculature is usually chaotic and generally unable to meet the requirements of the growing tumour, generating pockets of hypoxia.[109] These angiogenic cues result in the expression of growth factors such as VEGF that stimulate the sprouting of new blood vessels in a haphazard and disorderly manner. Moreover, these blood vessels are often leaky with uneven blood flow and are unable to carry nutrients or drugs efficiently to the TME.[117]

A number of recent studies have examined the role of 15-LOX-1 expression on the vasculature. The enzyme has been implicated as a factor that both activates and inhibits angiogenesis in different in vitro and in vivo models (Figure 4). In a hypoxia-induced retinal neovascularization (RNV) model, 15-LOX-1 expression showed anti-angiogenic properties by inhibiting the expressions of VEGF-A, vascular endothelial growth factor receptor-2 (VEGF-R2) and endothelial nitric oxide synthase (eNOS) in rat microvascular endothelial cells (RMVECs) in vitro.[118] Corroborating this, intravitreous injection of adenoviral-15-LOX-1 in a mouse model of oxygen-induced retinopathy (OIR) significantly inhibited RNV and down-regulated VEGF-A expression.[119] Mechanistically, the inhibition of RNV in the presence of 15-LOX-1 was reported to be via the up-regulation of PPAR-γ and down-regulation of VEGFR-2 expressions.[120] Similarly, in a rabbit skeletal muscle system, an anti-angiogenic effect was ascribed to 15-LOX-1 via the inhibition of capillary perfusion, vascular permeability, vasodilatation, increase in capillary number due to the reduced mRNA expressions of $VEGF\text{-}A_{165}$, PlGF-2 and VEGF-R2 together with reduced NO bioactivity.[121]

An increasing amount of evidence supports that lipid products of the 12/15-LOX pathway in mice (which includes a mixture of 12-HETE and 15-HETE using AA as substrate) are involved in the pathogenesis of retinal microvascular dysfunction thereby implicating a role in angiogenesis. 12/15-LOX plays a role in the development of pathological RNV, which was reduced in mice lacking 12/15-LOX or treated with the LOX inhibitor baicalein.[122] In diabetic mice,

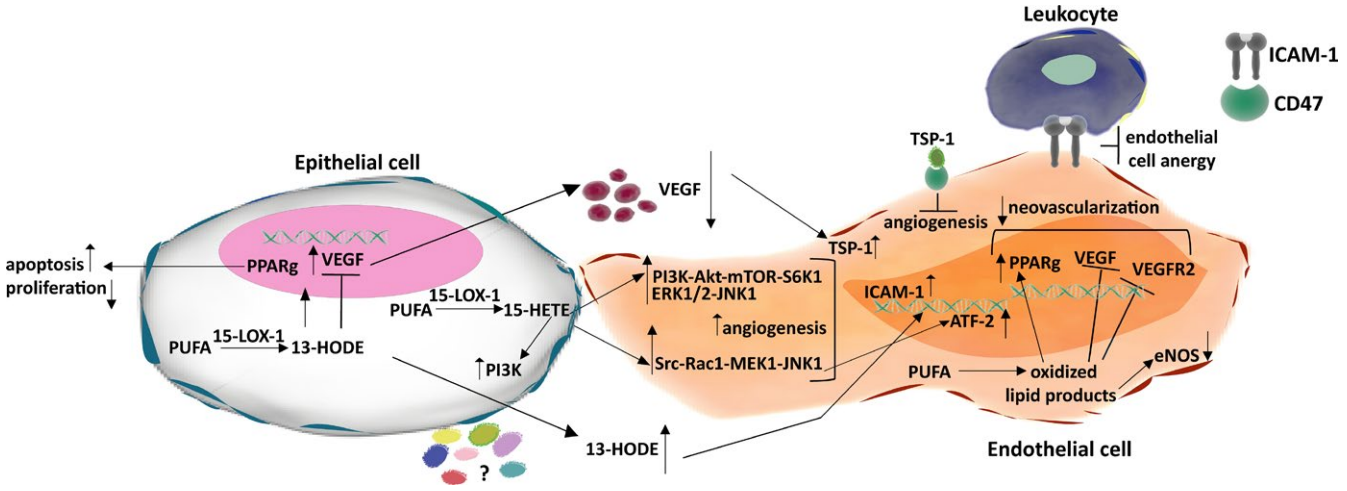

FIGURE 4 Implications of 15-LOX-1 in angiogenesis in different models. 15-LOX-1 has been implicated as a factor that both activates and inhibits angiogenesis. Expression of 15-LOX-1 in ECs reduced angiogenesis by reducing VEGF-A, VEGF-R2 and eNOs mRNA, and NO bioactivity, in vitro. In vivo, down-regulation of VEGFR-2 expression was via the upregulation of PPAR-γ. 13-HODE produced by 15-LOX-1 expressing cancer cells was shown to inhibit angiogenesis through enhanced expression of thrombospondin-1 (TSP-1) and ICAM-1 in ECs. Increased ICAM-1 expression may increase the recruitment of leukocytes and reduce endothelial cell anergy. On the other hand, 15-HETE was shown as a tumourigenic factor in epithelial cells, and a pro-angiogenic factor in ECs by activating the PI3K pathway. 15-HETE was also found to mediate EC migration, tube formation and angiogenesis through enhanced ATF-2 activity via the mitogen-activated protein kinase (MAPK, Src, Rac1, MEK1, JNK1) cascade. The other PUFA metabolites generated by 15-LOX-1 activity need to be determined in order to clarify the context-dependent action of the enzyme

12-HETE and 15-HETE were indicated to activate vascular NADPH oxidase, leading to overproduction of ROS, with subsequent activation of VEGF-R2 signalling and disruption of retinal endothelial cell barrier.[123] 15-HETE was also implicated as a pro-angiogenic factor by stimulating human dermal microvascular endothelial cell (HDMVEC) tube formation and migration in vitro and angiogenesis in vivo via the PI3K-Akt-mTOR-S6K1 signalling axis.[124] In addition, under hypoxic conditions, 15-HETE production was higher in human neonatal vessels compared to the normoxic condition.[125] Further studies showed that hypoxia could induce the expression of 15-LOX-1 and the production of 15-HETE, which in turn stimulated the migration and tube formation of human retinal microvascular endothelial cells (HRMVEC) through Src-dependent Rac1-mediated MEK1 stimulation.[126,127] Additionally, Singh et al have shown that by inducing the expression of HMG-CoA reductase, 15-HETE (produced through the activity of 12/15 LOX in mice) could facilitate the farnesylation and translocation of Rac1 to the plasma membrane of human dermal microvascular endothelial cell (HDMVECs) where it became activated and induced angiogenesis in response to hind-limb ischaemia.[128] 15-HETE was also shown to induce angiogenesis in endothelial cells derived from adipose tissue by up-regulating the production of CD31 and VEGF through PI3K/Akt/mTOR signalling in rats.[129] However, 15-oxo-ETE, the 15-LOX-1 metabolite that is produced from 15-HETE by macrophage-derived 15-Hydroxyprostaglandin dehydrogenase (15-PGDH), was shown to inhibit the proliferation of human vascular vein endothelial cells by suppressing DNA synthesis, implicating a potential angiostatic role.[130]

The effects of 15-LOX-1 expression on neo-angiogenesis have been recently examined in different cancer types. The overexpression of 15-LOX-1 in endothelial cells was shown to inhibit tumour growth and metastasis in a transgenic mouse model of mammary and Lewis lung carcinoma.[116] Additionally, the re-expression of 15-LOX-1 in HCT116, HT29 and LoVo colon cancer cells inhibited epithelial VEGF expression and the conditioned medium (CM) from these cells inhibited endothelial cell tube formation through, at least in part, a decrease in the expression and stability of HIF-1α.[114] On the other hand, 15-LOX-1 over-expression in the human prostate cancer cell line PC-3 was shown to increase the expression of VEGF in vitro and increase angiogenesis in subcutaneous xenografts.[131] Complicating the story even further, recently, 15-LOX-1 over-expression in PC-3 cells was shown to reduce angiogenesis through a ubiquitin-mediated enhanced degradation of HIF-1α and a consequent lower expression of VEGF-A mRNA.[132] Supporting the anti-angiogenic role of 15-LOX-1, we have recently shown that re-expression of 15-LOX-1 in HCT-116 and SW-480 CRC cell lines and LNCaP prostate cancer cells reduced the expression and secretion of VEGF-A in both normoxic and hypoxic conditions and CM from these cells decreased endothelial cell motility and tube formation.[133] Moreover, 15-LOX-1 CM treated mouse aortic rings showed significantly less sprouting with a more organized (less chaotic) structure of vascular network.[133] Mechanistically, endothelial cells treated with CM from 15-LOX-1 overexpressing CRC cell lines showed enhanced expression of Thrombospondin-1 (TSP-1), a matrix glycoprotein known to strongly inhibit neovascularization.[133] TSP-1 interacts with a vast number of different proteins, many of which play important roles in extracellular matrix remodelling, interactions between cells and the cell and extracellular matrix, motility and vascular normalization.[134] The same cells also showed enhanced expression of the cell adhesion

molecule ICAM-1. Endothelial cell-leukocyte interactions are mediated by the expression of CAMs, which may be reduced in tumour associated endothelial cells.[135,136] A reduction in adhesion proteins such as ICAM-1 can lead to endothelial cell anergy, causing reduced recruitment of immune cells to the TME and thereby immune suppression.[137] Treatment of HUVECs with 13-HODE mimicked most of the anti-angiogenic effects of 15-LOX-1.[133] Therefore, these data suggest that 15-LOX-1 related metabolites have the potential to be used as a therapeutic option to drive antitumour immunity through immune cell infiltration.

7 | FUTURE PERSPECTIVES

To date, the 15-LOX-1 field has attributed both pro- and anti-inflammatory as well as pro- or anti-tumourigenic roles to the enzyme. Such conflicting observations may due to the different biological effects of the many lipid mediators generated by the 15-LOX-1 pathway, which have not yet been fully elucidated.[138] It should also be noted that separate 12-LOX and 15-LOX enzymes do not exist in rodents, and 12/15-LOX, the mouse homolog of 15-LOX-1, has opposing functions with 15-LOX-1. Therefore, 12/15-LOX gene knockouts are likely to give limited and controversial results in human disease models. Additionally, the controversies between data published from different labs, or even from the same group may have resulted from differences in the expression of the enzyme and availability of substrates, which may affect the type of bioactive lipids produced in different tissues in a spatial and temporal manner. Furthermore, attempts to re-express the enzyme should also be context, tissue-type and disease dependent. For instance, lack of 15-LOX-1 expression in cancer cells is associated with their ability to escape terminal differentiation, while 15-LOX-1 and its downstream pathways are involved in the differentiation of nasal epithelial cells into a goblet cell/mucus-producing epithelium, and therefore contribute to pathology of chronic inflammatory airway diseases.[139,140]

Considering that the expression of 15-LOX-1 is lost in many different tumour types and strong data in recent years establishing an anti-tumourigenic role of 15-LOX-1, it is not surprising that there has been a lot of interest to understand the differential regulation of *ALOX15* in various types of cancers. However, the results are far from sufficient to indicate a general mechanism of repression of gene expression or to explain the interplay between the regulatory factors. Furthermore, the exact mechanisms underlying the transcriptional reactivation of 15-LOX-1 remains unknown in terms of the transcription factors that bind to the 15-LOX-1 promoter in different types of tumours. The direct effect of STAT-6 on 15-LOX-1 transcription is also questionable, since STAT-6 does not contribute to transcriptional reactivation by HDACi's in colon cancer cell lines.[141] At this point, identification of the specific components of HDAC-containing complexes, determination of the specific functions of HDACs within these complexes, and the molecular and biological consequences of pharmacological inhibition of these HDACs are necessary for different tumour types. For example, while existing HDACi's are effective for the treatment of a relatively small population of patients with defined haematological malignancies, they are not useful for the treatment of most other tumours.[142] Therefore, generation of target specific HDACi's with increased delivery and diffusion properties and less toxicity is needed. Moreover, use of methylation inhibitors together with specific HDACis might be an effective strategy for the re-expression of 15-LOX-1 in certain types of tumours, like CRC.

To the best of our knowledge, post-transcriptional regulation of 15-LOX-1 in human tumour has not been studied yet. Additionally, translational regulation of human 15-LOX-1 is not known although these mechanisms are well defined for rabbit 15-LOX-1.[143,144] Better understanding of the regulation of 15-LOX-1 expression in transcriptional, post-transcriptional and translational levels might help to understand the specific molecular mechanisms that control 15-LOX-1 expression in different types of human cancers. On the other hand, detailed analysis of *ALOX15* gene polymorphisms and mutations located in the coding or regulatory region of the gene and the contribution of these SNPs and/or mutations towards the expression of 15-LOX-1 in a cell type specific manner need to be examined. These data may help to develop proper diagnostic and therapeutic strategies in the treatment of human diseases, especially cancer.

8 | CONCLUSIONS

There is no doubt that lipids are crucial in signalling and cellular physiology in both health and disease. The importance of lipid metabolizing LOXs in the generation of pro-inflammatory mediators and more recently the pro-resolution mediators have firmly established these enzymes as important players in determining disease outcomes and re-establishing homeostasis.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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