Journal of Clinical and Translational Hepatology **2026** vol. 14(3) | 344–357
DOI: 10.14218/JCTH.2025.00502

Review Article

Advancements in Understanding the Role of Oxylipins in Liver Injury and Liver Failure

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Received: September 26, 2025 | **Revised:** December 29, 2025 | **Accepted:** January 22, 2026 | **Published online:** February 10, 2026

Abstract

End-stage liver disease (ESLD) is characterized by a dramatic deterioration of liver function, frequently accompanied by systemic inflammatory storms and multiple organ failures. Central to the onset and progression of ESLD, systemic inflammation arises from complex interactions among various inflammatory signaling molecules and immune cells within and beyond the liver. As key inflammatory modulatory molecules, bioactive oxylipins have been increasingly recognized for their complex molecular mechanisms implicated in various diseases. This review aims to summarize recent findings regarding the molecular and immunological mechanisms through which oxylipins contribute to the development of liver injury and failure, with emphasis on both substantial intrahepatic and extrahepatic immune and inflammatory dysregulation associated with ESLD. Furthermore, this review discusses the translational potential of targeting oxylipins for clinical diagnosis, prognosis, and therapeutic intervention in ESLD.

Citation of this article: Su X, Yimamu A, Tu S, Hao M, Bi H, Liu T, *et al*. Advancements in Understanding the Role of Oxylipins in Liver Injury and Liver Failure. J Clin Transl Hepatol 2026;14(3):344–357. doi: 10.14218/JCTH.2025.00502.

Introduction

The high mortality of end-stage liver disease (ESLD) is a global public health problem.[1] The exact pathophysiological mechanism remains elusive, involving a multitude of complex processes, including immune dysregulation and persistent inflammation, which further contribute not only to an increased risk of infection but also to a poor prognosis.[2,3] Inflammation plays a pivotal role in ESLD progression. It triggers the activation of immune cells, such as Kupffer cells (KCs), natural killer cells, and T lymphocytes,[4,5] leading to the release of cytokines, such as tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukins, and CXC motif chemokine ligand 12, as well as other inflammatory mediators, such as lipid metabolites derived from fatty acids.[6,7] These bioactive lipids are potent inflammation regulators and thus play critical roles in the pathogenesis of ESLD.

There are various types of bioactive lipids, including polyunsaturated fatty acids (PUFAs), lysoglycerophospholipids, sphingolipids, phytosterols, carotenoids, phenolic lipids, and endocannabinoids, etc., and their generation and metabolism exhibit considerable complexity.[8,9] These widely distributed lipids have multiple functions in the liver and play a crucial role in the regulation of hepatic signal transduction and metabolism. They regulate biological processes such as cell proliferation, differentiation, and apoptosis by binding to receptors on a wide range of hepatic cell subpopulations. Among these lipid mediators, oxylipins, which are oxygenated derivatives of PUFAs, are drawing increasing attention for their ability to orchestrate immune cell behavior and modulate inflammatory processes and immune responses.[10]

Recent studies have provided mounting evidence that oxylipins play important roles in the acute and chronic phases of liver diseases. During the acute phase of liver injury, eicosanoids are produced to induce pro-inflammatory responses and provide mitogenic signals to promote liver regeneration. Subsequently, pro-resolving oxylipins are produced to resolve inflammation, support tissue repair, and restore hepatic homeostasis.[10] In contrast, sustained injury is characterized by persistent eicosanoid-driven inflammation, notably through abnormal polarization of M2 macrophages, concurrently with diminished pro-resolving lipids. This deficiency in pro-resolving lipids leads to reduced phagocytosis, trapping the liver in a state of damaging chronic inflammation that ultimately promotes disease progression.[10] Ultimately, in progression to liver failure, a universal elevation of pro-inflammatory eicosanoids persists without timely resolution, compounded

Keywords: Liver injury; Liver failure; Oxylipin; Inflammation; Immune; Macrophage.
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by deficiency of pro-resolving lipids. This failure to resolve inflammation perpetuates hepatocyte damage and activates the circulating immune compartment, leading to severe systemic inflammation, multi-organ failure, and death.[11]

Therefore, bioactive oxylipins hold potential as therapeutic targets for liver diseases, particularly offering a promising approach to improve the prognosis of ESLD through modulation of lipid-mediated inflammatory signaling. This review aims to summarize the sources of bioactive oxylipins and their roles under various immune conditions, and to discuss the molecular and immunological mechanisms through which bioactive oxylipins contribute to the onset and progression of liver injury and failure, such as decompensated cirrhosis (DC) and acute-on-chronic liver failure (ACLF). Ultimately, we seek to provide insights that may inform future strategies for the prevention and treatment of ESLD based on the modulatory roles of oxylipins in inflammatory responses.

The types and sources of bioactive oxylipins

The n-6 PUFA (i.e., ω-6 PUFA) family of linoleic acid (18:2 n-6, LA), gamma-linolenic acid (18:3 n-6, γ-LNA) and arachidonic acid (20:4 n-6, AA), as well as the n-3 PUFA (i.e., ω-3 PUFA) family of alpha-linolenic acid (18:3 n-3, α-LNA), eicosapentaenoic acid (20:5 n-3, EPA), docosapentaenoic acid (22:5 n-3, DPA) and docosahexaenoic acid (22:6 n-3, DHA), serve as substrates for various oxidases to produce bioactive oxylipins, which mediate inflammatory responses.[12] The process of PUFA oxidation involves three major enzymatic pathways, namely cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) pathways. Each pathway comprises multiple enzymes that produce several bioactive lipids (Fig. 1A). The COX enzymes, such as COX-1 and COX-2, convert PUFAs into prostaglandins (PGs; e.g., PG-D/E/F/G/H/I) and thromboxane A2 (TXA_2).[13,14] Notably, COX-1 is constitutively expressed in most cells, serving as the primary source of prostanoids that fulfill essential housekeeping functions.[9,13] In contrast, COX-2 is induced by inflammatory stimuli, hormones, and growth factors, and is generally regarded as the primary source of prostanoids in inflammatory and proliferative diseases.[9,13,15] On the other hand, LOX enzymes, including 5-LOX, 12-LOX, 15-LOX, and LOXE3, produce leukotrienes (LTs; e.g., LTA/B/C/D/E) and hydroxyeicosatetraenoic acids (HETEs; e.g., 5/8/12/15-HETE).[16–19] Among them, 5-LOX is considered to be the primary contributor to LT production, and it is predominantly expressed by myeloid cells, including polymorphonuclear leukocytes (PMNs), B lymphocytes, monocytes, macrophages, dendritic cells, and mast cells.[20] Furthermore, these LOX enzymes also synthesize anti-inflammatory mediators such as lipoxins (LXs) and specialized pro-resolving mediators (SPMs), including resolvins (Rvs), protectins, and maresins (MaRs).[21,22]

The third oxidase family, CYP450 enzymes, is expressed primarily in organs such as the liver, kidney, brain, heart, and lung but is expressed relatively lowly in circulating cells.[23,24] Within the CYP450 superfamily, a subset of CYP2 isoforms is mainly responsible for epoxygenation.[25] For example, epoxyeicosatrienoic acids (EETs), including 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET, are produced from AA by the action of CYP2C and CYP2J. In parallel, epoxyeicosatetraenoic acids (EETs or EpETEs) are produced from EPA.[25] These EET metabolites are then further metabolized to dihydroxyeicosaprienoic acids by soluble epoxide hydrolases.[26] Another group of CYP enzymes, the CYP4s with ω-hydroxylase activity, convert AA to HETEs, including 16-HETE, 17-HETE, 18-HETE, 19-HETE, and 20-HETE. They also convert EPA to hydroxyeicosapentaenoic acids (HEPEs). Additionally, microsomal CYP enzymes react with AA to produce HETEs. Many of these lipid derivatives are unstable and undergo rapid conversion to other products through enzymatic and non-enzymatic actions.[27,28] Ongoing investigations are unraveling the diverse biological functions mediated by these lipid derivatives, with an expanding collection of structurally distinct species being systematically characterized.

Oxylipins are generated by various types of cells, including immune cells such as macrophages and neutrophils, as well as endothelial cells and adipocytes. Among these, SPMs are mainly produced via transcellular biosynthesis, with M2 macrophages and PMNs acting as key participants.[29] Leukotrienes are mainly biosynthesized by leukocytes from myeloblastic (neutrophils, eosinophils, and mast cells) and monoblastic lineages (monocytes and macrophages).[20,30] Anti-inflammatory LXs are formed by transcellular biosynthesis via multiple collaborating pathways in leukocytes (including eosinophils and monocytes), platelets, and epithelial cells.[18,21,29] Rvs are produced through the interactions of COX-2 and LOX activities in endothelial cells, leukocytes (including PMNs), and glial cells.[31–34] The differential expression of COX within inflammatory cells determines the production of different prostanoids, such as PGD_2 by mast cells and PGE_2 and TXA_2 by macrophages.[35] In addition, EETs are produced in the liver at biologically relevant levels and are also detected in the vasculature and cardiomyocytes.[9] In summary, the complexity of oxylipin biosynthesis arises from the dynamic interplay between diverse cell types and their microenvironment, where transcellular metabolism and spatial enzyme distribution collectively dictate the spectrum of bioactive lipid mediators and thus their functions in regulating inflammation, immune response, and tissue repair.

The modulatory roles of oxylipins in inflammatory responses

Classical eicosanoid metabolites, including PGs, LTs, and TXs, have been well-studied as inflammatory mediators. Generally, AA-derived pro-inflammatory 2-series PGs, 4-series LTs, and related lipid mediators exhibit substantially higher pro-inflammatory potency, whereas EPA-derived 3-series PGs, 3-series TXs, and 5-series LTs exert attenuated inflammatory bioactivity relative to their AA-derived homologs.[8,10,19] Despite their low physiological concentrations in the body, these eicosanoids exhibit profound biological activity: they can modulate cellular functions by binding to specific receptors, triggering signal transduction pathways within a short timeframe to elicit significant physiological effects. Among these, TXs promote hepatic microvascular constriction and stimulate the release of pro-inflammatory cytokines, causing platelet aggregation and leukocyte recruitment.[10,36,37] Prostaglandins, particularly PGE_2 and PGI_2, act as cytokine amplifiers and drive the switch between acute and chronic inflammation through multiple mechanisms, including enhancing cytokine release, intensifying innate immune responses to pathogen- and damage-associated patterns (PAMPs and DAMPs), differentiating immune cells into pro-inflammatory subsets, recruiting T helper cells, and increasing the expression of cytokine-induced pro-inflammatory genes.[11,38,39] Leukotrienes, such as LTB_4, can recruit leukocytes (especially neutrophils and macrophages) to sites of inflammatory or immune responses and induce these cells to produce pro-inflammatory cytokines, including TNF-α and interleukins (IL-1β/-6/-8).[40] On the other hand, LTB_4 also appears to promote immune defenses by modulating the functions of T lymphocytes (increasing proliferation and production of IL-2 and interferon-γ, suggesting enhanced Th1 cell activ-

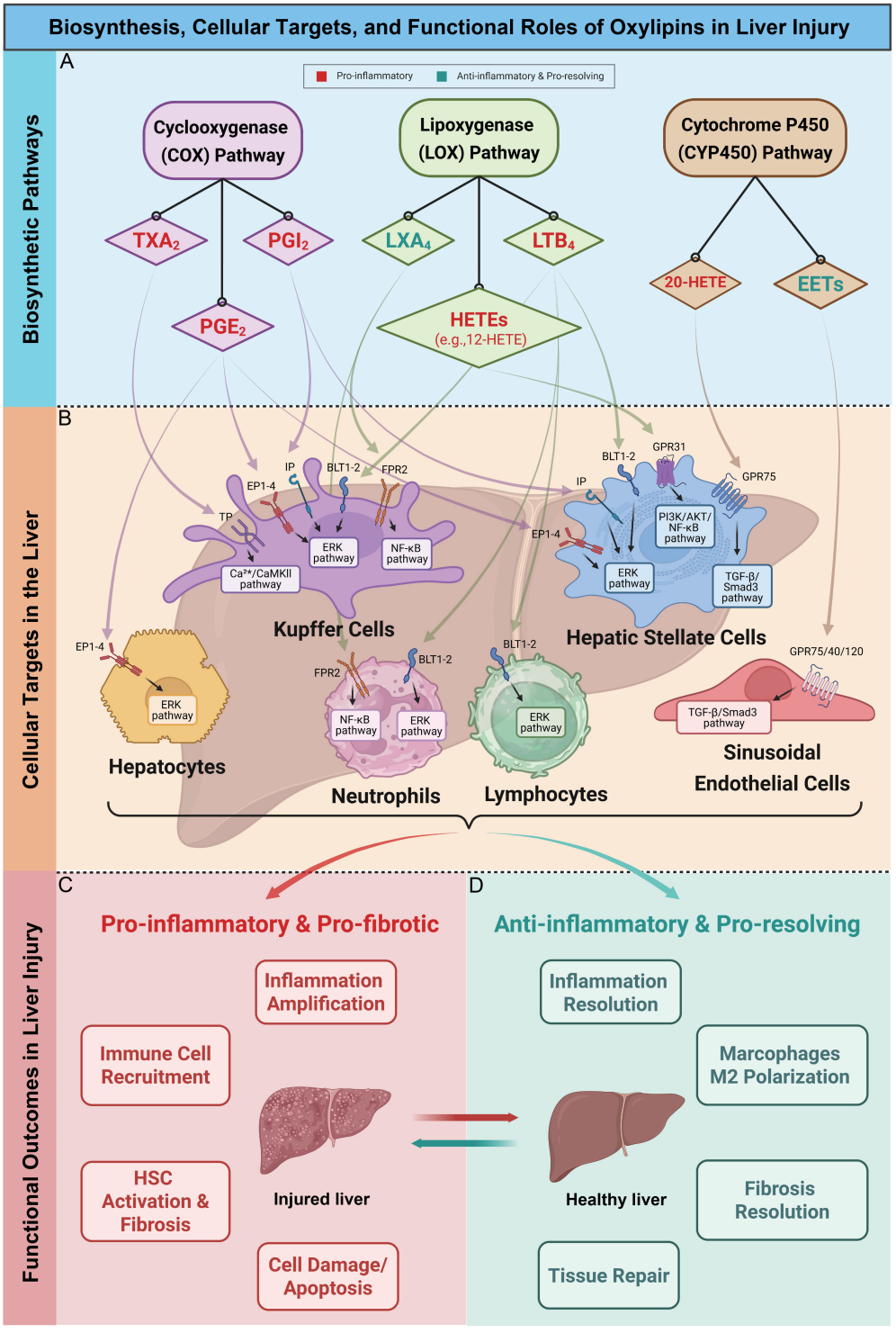

Fig. 1. Biosynthesis, cellular targets, and functional roles of oxylipins in liver injury. (A) Oxylipins are mainly synthesized via cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) pathways. Key pro-inflammatory oxylipins (red) and pro-resolving oxylipins (green) are highlighted. (B) Each oxylipin acts on liver cells through its corresponding receptors and signaling pathways. (C) Pro-inflammatory oxylipins promote liver injury by inducing the recruitment of immune cells, amplifying pro-inflammatory signaling, activating quiescent HSCs into collagen-secreting myofibroblasts, and triggering hepatocyte apoptosis. Pro-resolving oxylipins counteract these pathological processes by promoting inflammation resolution, driving macrophage polarization toward the anti-inflammatory M2 phenotype, facilitating fibrosis regression, and enhancing hepatic tissue repair, ultimately supporting the recovery of normal liver function. Figure created with BioRender. TXA_2, thromboxane A_2; PGE_2, prostaglandin E_2; PGI_2, prostaglandin I_2; LXA_4, lipoxin A_4; LTB_4, leukotriene B_4; HETEs, hydroxyeicosatetraenoic acids; EETs, epoxyeicosatrienoic acids; HSC, hepatic stellate cell; TP, thromboxane receptor; EP, prostaglandin E receptor; IP, prostaglandin I receptor; BLT, leukotriene B receptor; FPR, N-formyl peptide receptor; GPR, G-protein-coupled receptor.

ity), B lymphocytes (promoting differentiation and increasing immunoglobulin E production), and natural killer cells (augmenting cytotoxicity).[40]

The functions of non-classical eicosanoid metabolites, such as EETs and HETEs generated from AA, are less well understood, and warrant further investigation. Recent findings indicate that 20-HETE can stimulate endothelial cells to release inflammatory IL-4, IL-8, and IL-13.[41] Adipocytes challenged by 12/15-LOX produced 12-HPETE and 12(S)-HETE and also augmented the expression of pro-inflammatory cytokines such as TNF-α, MCP-1, IL-6, and IL-12p40.[42] Interestingly, 5-HETE derived from AA can either be metabolized to inflammatory LTs by 5-LOX,[43] or, conversely, be converted into anti-inflammatory LXs and their derivatives by 12-LOX. LXs have been shown to exert anti-inflammatory effects by enhancing macrophage-mediated clearance of apoptotic neutrophils, thereby promoting the resolution of inflammation.[44,45] Moreover, EETs produced by CYP2 enzymes also have anti-inflammatory effects, which can reduce the expression of vascular cell adhesion molecule in endothelial cells and inhibit the secretion of cytokines by macrophages.[46]

It has been demonstrated that AA-derived HETEs, EPA-derived HEPEs, and DHA-derived hydroxyeicosahexaenoic acids (HDHAs), as intermediate precursors in SPM biosynthetic pathways, can be further converted into bioactive SPMs with anti-inflammatory and pro-resolving functions.[47] These SPMs include LXs (e.g., EPA-derived LXA_5, AA-derived LXA_4 and LXB_4), Rvs (RvDs and RvEs), MaRs, and neuroprotectin D1).[10] By binding to specific receptors, these SPMs activate or inhibit intracellular signaling pathways, not only reducing excessive inflammatory responses but also actively driving the resolution of inflammation (e.g., enhancing efferocytosis and promoting tissue repair) to facilitate tissue homeostasis restoration.[11]

Oxylipins typically bind to and activate specific members of the G protein-coupled receptor (GPCR) family. The diversity of GPRs allows oxylipins to target signaling pathway activation based on distinct receptor combinations, resulting in diverse cellular functions. Taking PGE_2 binding to prostanoid E receptors (EPs; EP1–EP4) as an example, EP1 and EP2 require higher concentrations of PGE_2 to initiate signaling cascades, whereas EP3 and EP4 can be stimulated at lower ligand concentrations.[48] Stimulation of EP2 and EP4 receptors leads to the activation of ERK1/2, AKT, NF-κB, and β-catenin signaling pathways, ultimately enhancing cell survival and migration.[49] Most splice variants of EP3 function as Gi-coupled receptors that inhibit adenylate cyclase and modulate anti-inflammatory responses, while EP1-mediated signaling involves the stimulation of intracellular calcium.[50] Additionally, Rvs (including RvD and RvE), MaRs, and LXA_4 share the same receptor ALXR (also known as N-formyl peptide receptor 2, FPR2), while EETs and HETEs interact with GPCRs such as GPR75, GPR40, and GPR120.[51–55] These interactions highlight the complex and specific roles of oxylipins in regulating inflammatory responses and cellular functions, as summarized in Figure 1B and C. For more extensive coverage of the regulatory functions of oxylipins, see Chiurchiù's and Calder's comprehensive review.[39,40]

Oxylipins and key associated lipids in liver injury and liver failure

Recent studies have documented altered oxylipid signatures in patients with liver cirrhosis or ACLF.[56–58] The study based on the European CANONIC Cohort of ESLD observed a generalized suppression of lipids in cirrhosis patients, with sphingomyelin being linked to the acute decompensation (AD) stage and cholesteryl esters and lysophosphatidylcholine (LPC) correlated with ACLF pathogenesis.[58] Another study of the European CANONIC Cohort identified 16 plasma oxylipins significantly associated with cirrhotic status.[59] Within these compounds, LTE_4 and 12-hydroxyheptadecatrienoic acid (12-HHT) can be used to identify ACLF patients, while LTE_4 levels correlate with ACLF severity and inflammation markers. Furthermore, the combination of LTE_4, LXA_5, and 12,13-epoxy-9-keto-10(trans)octadecenoic acid (EKODE) was linked to short-term mortality in ACLF patients.[59] Furthermore, albumin from patients with AD exhibited lower content of PUFAs and PGE_2, as well as lower levels of monohydroxy FA precursors of anti-inflammatory/pro-resolving lipid mediators, such as 15-HETE, compared to healthy subjects.[60] These studies clearly show that the pathogenesis of ACLF or cirrhosis is closely associated with complex lipidomic modulation, revealing a complex interplay between lipid metabolism and disease progression.

Additionally, some studies investigated lipidomic modulation in patients with hepatitis B virus (HBV) infection, which significantly contributed to DC and ACLF in China and other Asian countries. Patients with HBV-ACLF exhibited increased levels of pro-inflammatory n-6 PUFA derivatives, including 8,9-EET, $PGD_{1/2}$, PGJ_2, 11β-$PGF_{2α}$, 11β-PGE_2, LTB_4, LTD_4, LTF_4, 11-trans-LTE_4, $TXB_{1/2/3}$ alongside various HETE compounds (5/8/9/11/12/15-HETE). Consistently, elevated EPA-derived metabolites (such as RvE1 and 5/8/9/12/15-HEPE) and DHA-derived metabolites (such as protectin D1, RvD1/3/5, and 4/8/10/11/13/14/16/17/20-HDHA) were also observed in HBV-ACLF patients compared to HBV-DC patients.[61] Furthermore, a recent study demonstrated a significant increase in eicosanoid production in HBV-ACLF patients, including 9-hydroxyoctadecadienoic acid (9-HODE), 13-HODE, 12,13-dihydroxyoctadecenoic acid (12,13-DiHOME), and 9,10-DiHOME.[62] In patients with HBV-related hepatocellular carcinoma (HCC), eight LA-derived and AA-derived eicosanoids were found to be significantly elevated, of which 9- and 13-HODE in particular have shown potential as HCC biomarkers.[63] In another study to portray oxylipin profiles related to chronic HBV infection progression, the authors observed increased levels of CYP450-derived 9,10-DiHOME, 12,13-DiHOME, and 14,15-dihydroxyeicosatrienoic acid in HBV-related liver cirrhosis and HCC patients.[64] In addition to their potential as HBV-related ESLD markers, a recent clinical trial revealed that removing pro-inflammatory eicosanoids by hemoperfusion adsorption was associated with favorable outcomes in ACLF patients.[65]

Scientists also found that patients with alcohol-related liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD) had different oxylipin profiles.[66] A 2022 cohort study revealed that severe NAFLD patients exhibited significantly elevated plasma levels of specific oxylipins, including both pro-inflammatory $PGF_{2α}$ and pro-resolving LXB_4 and MaR-1.[67] The authors found that serum oxylipins, including 8,9-dihydroxyeicosatrienoic acid, 4-hydroxydocosahexaenoic acid, 14-hydroxydocosahexaenoic acid, LXA_4, and 12S-HETE, were decreased in alcoholic hepatitis patients compared to those with alcohol use disorder.[68] Of particular interest, elevated 20-HETE levels were associated with increased hepatic steatosis, polymorphonuclear neutrophil infiltration, as well as higher 90-day mortality in patients with ALD.[68] Another study reported that 13-HODE was markedly elevated in patients with moderate alcoholic hepatitis, distinguishing it from mild alcohol-associated liver injury.[69] Collectively, these studies highlighted the potential of oxylipins as dynamic biomarkers, not only for tracking ALD/NAFLD progression but also for distinguishing disease severity and subtypes.

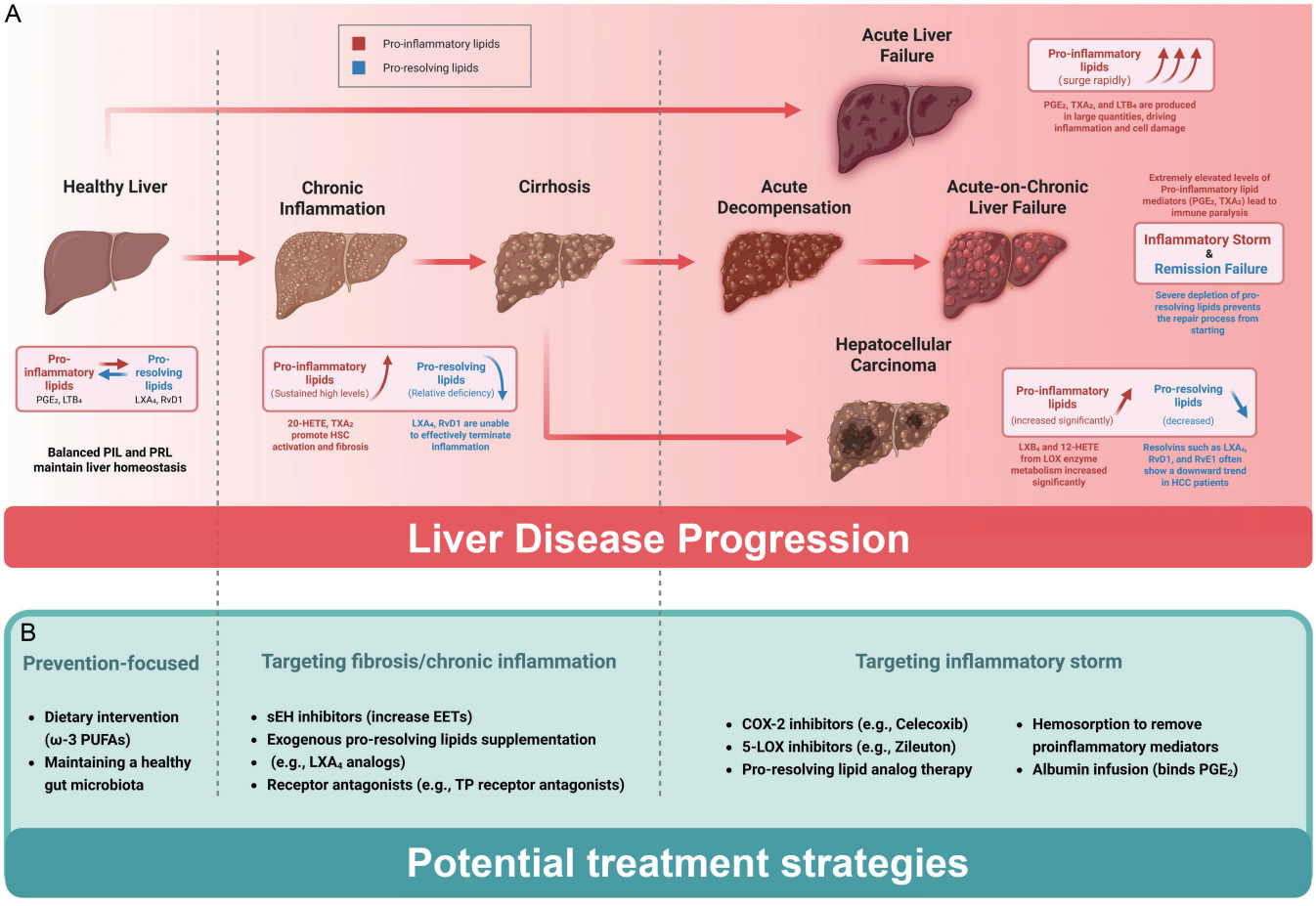

Fig. 2. Dynamic changes of oxylipins and therapeutic opportunities during liver disease progression. (A) As liver pathology advances from chronic inflammation to cirrhosis, acute-on-chronic liver failure, or hepatocellular carcinoma, a general trend characterized by elevated levels of pro-inflammatory oxylipins (e.g., 20-HETE, TXA_2, PGE_2) and reduced abundance of pro-resolving oxylipins (e.g., RvD1, RvE1) is observed. These dynamic shifts highlight the potential of oxylipins as biomarkers for tracking disease severity and as therapeutic targets. (B) Targeting oxylipin metabolism and homeostasis, therapeutic strategies for liver diseases may be constructed as follows: prophylactic approaches prioritize maintaining oxylipin balance via ω-3 PUFA supplementation to enrich pro-resolving oxylipin precursors and modulate healthy gut microbiota; interventions against fibrosis and chronic inflammation focus on restoring the pro-inflammatory/pro-resolving oxylipin equilibrium by using sEH inhibitors to elevate EET levels, using exogenous pro-resolving lipid analogs and receptor antagonists; and management of inflammatory storms relies on mitigating excessive pro-inflammatory oxylipin activity by using COX-2/5-LOX inhibitors, pro-resolving lipid analogue therapy, hemadsorption to clear pro-inflammatory mediators, and albumin infusion to sequester pro-inflammatory PGE_2. Figure created with BioRender. HSCs, hepatic stellate cells; PGE_2, prostaglandin E_2; LTB_4, leukotriene B_4; LXA_4, lipoxin A_4; RvD1, resolvin D1; 20-HETE, 20-hydroxyeicosatetraenoic acid; TXA_2, thromboxane A_2; 12-HETE, 12-hydroxyeicosatetraenoic acid; RvE1, resolvin E1; PUFAs, polyunsaturated fatty acids; EETs, epoxyeicosatrienoic acids; TP, thromboxane receptor; COX-2, cyclooxygenase-2; 5-LOX, 5-lipoxygenase.

Liver disease-specific lipid signatures can also be found in circulating extracellular vesicles (EVs). For instance, low levels of circulating EVs were found in patients with cirrhosis, regardless of severity, and altered EV lipid content showed considerable correlation with disease status.[70] Specialized lipid mediators from EVs, including 18-HEPE, RvEs, RvDs, and MaRs, were lower in ACLF patients than in AD patients without ACLF. In AD, levels of EV-harbored RvE1 correlated closely with CD5L levels. Moreover, functional studies in macrophages indicated a positive feedback loop between CD5L and RvE1 biosynthesis that orchestrated the resolution of inflammation. This study suggested that the dramatic alteration of circulating EV contents along with loss of anti-inflammatory molecules was closely related to disease progression during the development of AD-ACLF.[70] The oxylipin markers associated with ESLD progression were visualized in Figure 2A, and their potential diagnostic implications have been summarized in Table 1.[58–65,67–70]

Collectively, the oxidative lipidomic analyses of clinical samples from the European CANONIC Cohort of ESLD patients, Chinese HBV-related ACLF patients (or patients from other Asian countries), as well as individuals with ALD or NAFLD, demonstrate that oxylipins exhibit considerable clinical diagnostic potential as etiology-specific, stage-sensitive, and prognosis-associated biomarkers. Across geographically diverse populations and heterogeneous etiologies, these oxylipin signatures exhibit consistent associations with disease progression, organ dysfunction, and clinical outcomes, underscoring their robustness as universal diagnostic tools. Collectively, these findings validate the significant clinical diagnostic utility of oxylipins and support their potential integration into routine clinical practice to enhance diagnostic precision, optimize risk stratification, and guide the personalized management of patients with liver injury and liver failure. Nevertheless, the clinical application of oxylipins in ESLD diagnosis remains hampered by several challenges, including insufficient granularity in disease subgroup stratification in current studies and limitations in analytical meth-

Table 1. Summary of lipidomic signature and oxylipin markers associated with ESLD progression

Liver diseases	Oxylipid markers	Direction of change	Clinical/Therapeutic significance	References
AD-ACLF (European cohort)	Sphingomyelin	Decreased in AD	Linked to the stage of AD	58
	Cholesteryl esters, lysophosphatidylcholine (LPC)	Decreased in ACLF	Correlated with ACLF pathogenesis	
	Albumin-bound PGE_2, precursors of pro-resolving mediators (e.g., 15-HETE)	Decreased in AD	Lower levels of pro-resolving lipid precursors compared to healthy subjects	60
	LTE_4, 12-HHT	LTE_4 increased and 12-HHT decreased in ACLF	Discriminated patients with ACLF from those without. LTE_4 levels correlate with ACLF severity and inflammation markers	59
	LXA_5, EKODE	EKODE increased and LXA_5 decreased in ACLF	Linked to short-term mortality in ACLF patients	
	18-HEPE, RvEs, RvDs and MaRs	Decreased in AD	Lower EV levels compared to AD patients. CD5L-RvE1 positive feedback loop may orchestrate inflammatory resolution	70
HBV-cirrhosis/ HCC	9,10/12,13-DiHOME, 14,15-DiHETrE	Increased	Associated with the progression of chronic HBV infection	64
HBV-HCC	8 LA-/AA-derived eicosanoids (specifically 9-HODE and 13-HODE)	Increased	Potential biomarkers for HCC	63
HBV-ACLF	n-6 PUFA derivatives: 8,9-EET, $PGD_{1/2}$, PGJ_2, 11β-$PGF_{2\alpha}$, 11β-PGE_2, LTB_4, LTD_4, LTF_4, 11-*trans*-LTE_4, $TXB_{1/2/3}$, 5/8/9/11/12/15-HETE	Increased	Promote inflammatory response, associated with disease severity	61
	EPA- derived: RvE1, 5/8/9/12/15-HEPE; DHA-derived: Protectin D1, RvD1/3/5, 4/8/10/11/13/14/16/17/20-HDHA	Increased	Possible compensatory anti-inflammatory or pro-resolving response, still associated with ACLF	61
	9-HODE, 13-HODE, 9,10/12,13-DiHOME	Increased	Reflect active eicosanoid metabolism	62
	Eicosanoids	Increased	Hemoperfusion adsorption of pro-inflammatory eicosanoids is associated with a favorable outcome in ACLF patients	65
NAFLD	$PGF_{2\alpha}$, LXB_4, MaR-1	Increased	Shows complex simultaneous changes in pro-inflammatory and pro-resolving mediators, reflecting disease state	67
AH	8,9-DiHETrE, 4-/14-HDoHE, LXA_4, 12S-HETE	Decreased	Lower levels compared to patients with alcohol use disorder may reflect metabolic disruption or consumption	68
	20-HETE	Increased	Associated with hepatic steatosis, polymorphonuclear neutrophil infiltration, and 90-day mortality	68
	13-HODE	Increased	Distinguishes moderate AH from mild alcohol-associated liver injury	69

AD, acute decompensation; ACLF, acute-on-chronic liver failure; PG, prostaglandin; HETE, hydroxyeicosatetraenoic acid; LT, leukotriene; 12-HHT, 12-hydroxyheptadecatrienoic acid; LX, lipoxin; EKODE, 12,13-epoxy-9-keto-10(trans)octadecenoic acid; HEPE, hydroxyeicosapentaenoic acid; Rv, resolvin; MaR, maresin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; DiHOME, dihydroxyoctadecenoic acid; DiHETrE, dihydroxyeicosatrienoic acid; LA, linoleic acid; AA, arachidonic acid; HODE, hydroxyoctadecadienoic acid; PUFA, polyunsaturated fatty acid; EET, epoxyeicosatrienoic acid; TX, thromboxane; NAFLD, non-alcoholic fatty liver disease; AH, alcoholic hepatitis; HDoHE, 4-hydroxydocosahexaenoic acid.

odologies (see detailed discussions in the Future Prospects section).

Mechanism of oxylipins involved in liver injury and liver failure

The pro-inflammatory role of COX-2 and its major oxylipin products in liver injury has been extensively studied. During acute liver injury, the upregulation of COX-2 expression leads to the production of PGs and TXs, which can exacerbate inflammation and hepatocyte damage.[71–74] Conversely, inhibition of COX-2 can protect the liver from ischemia-reperfusion (I/R) injury by reducing neutrophil infiltration.[75–77] Furthermore, several studies have shown that COX-2 is highly expressed in activated hepatic stellate cells (HSCs, a central cell type driving liver fibrosis),[78,79] and it modulates MCP-1 expression via the prostaglandin-cAMP pathway, thereby enhancing the pro-inflammatory potential of HSCs.[80] Consistently, COX-2 induction and increased PGE_2 production are found to be closely associated with platelet-derived growth factor-stimulated proliferation and migration of HSCs.[81,82] Conversely, celecoxib-mediated COX-2 inhibition alleviates liver cirrhosis in thioacetamide (TAA) rat models by attenuating the COX-2/PGE_2/EP2/p-ERK signaling, which enhances intestinal epithelial barrier function by upregulating ZO-1 and E-cadherin, blocks inflammatory transport through the gut-liver axis, and ameliorates the progression of liver fibrosis.[83] In a lipopolysaccharide (LPS)/galactosamine-induced acute liver injury model, the reduction of PGE_2 levels mediated by the targeted expression of 15-hydroxyprostaglandin dehydrogenase diminished hepatocyte death.[84] A Chinese hepatitis B cohort study found that plasma PGE_2 levels were higher in ACLF patients, and these elevated PGE_2 levels were closely associated with systemic inflammation and disease severity.[85] Elevated concentrations of PGE_2 have also been observed in patients with AD.[86] *In vitro* experiments demonstrated that plasma from patients with AD and ESLD suppressed macrophage pro-inflammatory cytokine secretion and bacterial killing in a PGE_2-dependent manner, which was mediated by EP2.[86] Additionally, another investigation revealed that monocyte dysfunction in patients with DC was also mediated by PGE_2 via its EP4 pathway.[87]

However, certain PGs exhibit a dual role in liver physiology. While they can induce inflammation and aggravate liver injury, there is emerging evidence suggesting that they may also possess hepatoprotective effects and facilitate hepatocyte regeneration. Notably, *in vitro* studies have demonstrated that COX-2-derived PGE_2 inhibits both basal and transforming growth factor-β1-mediated collagen synthesis in HSCs, a key mechanism mitigating fibrogenesis.[88] Interestingly, depletion of PGE_2 synthase (PGES) 1 in a mouse non-alcoholic steatohepatitis (NASH) model leads to liver inflammation and hepatocyte apoptosis, showing increased TNF-α release upon LPS treatment.[89] Consistently, studies also demonstrated that knockout of COX-2 or administration of PGES inhibitors aggravated acetaminophen-induced liver injury.[71,90] On the other hand, it has been noted that PGE_2 exhibits hepatoprotective effects by inducing proliferation, which may be mediated by receptor isoforms.[91,92] For instance, neutrophil accumulation was inhibited by EP4 (a subtype of PGE_2 receptor) agonist treatment, which significantly alleviated hepatic I/R injury.[75] PGE_2 has been shown to reduce fat deposition in mouse primary hepatocytes exposed to palmitic acid (PA).[93] Furthermore, methionine-choline-deficient diet-fed mice lacking the PGI_2 receptor developed more severe progression of NASH, indicating that PGI_2 played a crucial role in the development and progression of steatohepatitis by modulating the inflammatory response.[94] In conclusion, the balance between these pro- and anti-inflammatory functions of prostaglandins (particularly PGE_2), as well as their effects on cell growth and apoptosis, determines their role in the progression of liver disease. A comprehensive understanding of these intricate and delicate balances is crucial for the development of effective therapeutic strategies against liver diseases, including ACLF and others.

In addition to COX-2-derived lipids, oxylipins produced by liver-enriched CYP450 also play crucial pathophysiological roles. The most abundant CYP450-derived oxylipin is 20-HETE, which accounts for 50% to 70% of eicosanoids produced in the liver.[95] The pleiotropic effects of 20-HETE encompass regulation of vascular tone, promotion of inflammatory response, and modulation of cell proliferation and apoptosis. 20-HETE has been found to induce hepatic fibrosis mainly via the transforming growth factor-β/Smad3 pathway.[96] Moreover, a lipidomic analysis revealed that 20-HETE was the predominant eicosanoid compound in cirrhosis patients, with levels even higher than those of PGs and TXs, suggesting its potential significance in cirrhotic progression.[97] Recent genome-wide association studies have linked GPR75 variants to reduced risk of hepatic steatosis.[98,99] Mechanistically, 20-HETE activates GPR75-dependent pathways, promoting vasoconstriction and hypertensive phenotypes.[54,100,101] Collectively, these findings suggest that the 20-HETE-GPR75 axis may serve as a critical mediator in the pathogenesis of liver fibrosis and portal hypertension. Future investigations are warranted to determine the physiological and pathological roles of hepatic 20-HETE, elucidate the functional interplay between GPR75 and liver disease progression, and evaluate the therapeutic potential of targeting this pathway in ESLD.

Higher expression of LOXs, including 5-LOX, 12-LOX, and 15-LOX, has been found in liver diseases.[102–104] LXs are generated from AA via biosynthetic pathways involving dual LOX combinations either by 5/15-LOX or by 5/12-LOX, and have been extensively studied preclinically for their anti-inflammatory effects or their roles in promoting resolution of inflammation.[105] LXA_4, the major physiological LX form, could promote apoptosis and inhibit proliferation, migration, and angiogenesis of HepG2 hepatocarcinoma cells stimulated by LPS or by macrophage-conditioned media.[105] However, LXA_4 has also been demonstrated to be involved in the induction of myeloid-derived suppressor cells after Treg depletion, which tunes tumor-associated inflammation and promotes tumor growth.[106] A study revealed that 12-LOX-mediated 12-HETE production was enhanced during I/R injury, and blockade of this pathway ameliorated I/R-induced liver dysfunction, inflammation, and cell death.[107] Moreover, activation of this pathway is also enhanced in NAFLD, where 12-HETE induces matrix metalloprotein expression by activating the PI3K/AKT/NF-κB pathway, thus leading to epithelial-mesenchymal transition and HCC recurrence in fatty liver more than in normal liver.[103] LTB_4 and LTC_4 are inflammatory lipid mediators derived from AA via 5-LOX oxidation, and they contribute to liver fibrosis by activating the extracellular signal-regulated protein kinase pathway in HSCs.[102] Moreover, hepatic 15-HETE production is disturbed in 3,5-diethoxycarbonyl-1,4-dihydrocollidine-treated mice, and reducing 15-HETE levels via inhibiting 15-LOX results in apoptosis.[108,109] Overall, these findings highlight the complex role of LOXs and relevant oxylipins in liver disease. The balance between these metabolites and their regulatory mechanisms is crucial for maintaining liver health and preventing disease progression. Table 2 lists some oxylipins and their known pathways involved in liver injury and liver failure.[54,68,71–77,80–83,85–94,96–103,105–109]

Table 2. Summary of oxylipin mechanisms in liver diseases

Oxylipin(s)	Enzyme(s)	Liver diseases	Mechanism of action	References
PGs & TXs	COX-2	Acute liver injury	COX-2 upregulation leads to production of PGs and TXs, exacerbating inflammation and hepatocyte damage; COX-2 Inhibition reduces neutrophil infiltration and I/R injury	71–77
PGs	COX-2	Liver fibrosis	COX-2 modulates MCP-1 expression via PG-cAMP pathway	80
PGE_2	COX-2/ PGES1	ACLF, AD	Elevated in AD and ACLF, associated with systemic inflammation; Suppresses macrophage proinflammatory cytokine secretion and bacterial killing via receptor EP2; Mediates monocyte dysfunction via receptor EP4	85–87
		Liver fibrosis, liver cirrhosis	Increased PGE_2 is associated with PDGF-stimulated proliferation and migration of HSCs; PGE_2 inhibits both basal and transforming TGF-β1-mediated collagen synthesis in HSCs; Celecoxib-mediated COX-2 inhibition alleviates liver cirrhosis via COX-2/PGE_2/EP2/p-ERK signaling	81–83,88
		NASH, APAP-induced injury	Depletion leads to increased liver inflammation and apoptosis in NASH; Induces hepatocyte proliferation via receptor isoforms; Reduces fat deposition in hepatocytes; EP4 receptor agonist inhibits neutrophil accumulation, alleviating I/R injury	71,75,89–93
PGI_2	COX-2	NASH	Hepatoprotective; lack of its receptor leads to severe NASH	94
LXA_4	5/15- or 5/12-LOX	HCC	Anti-tumorigenic, promotes apoptosis and inhibits proliferation, migration, and angiogenesis in hepatocarcinoma cells; Pro-tumorigenic, induction of MDSCs, which promotes tumor growth	105,106
LTB_4, LTC_4	5-LOX	Liver fibrosis	Contribute to liver fibrosis by activating the ERK pathway in HSCs	102
12-HETE	12-LOX	NAFLD/HCC	12-LOX blockade ameliorates I/R induced liver dysfunction, inflammation, and cell death; In NAFLD, induces matrix metalloproteinase expression via PI3K/AKT/NF-κB pathway, leading to EMT and higher HCC recurrence	103,107
15-HETE	15-LOX	Cholestatic liver injury	Hepatoprotective; its reduction via 15-LOX inhibition results in hepatocyte apoptosis	108,109
20-HETE	CYP450	Liver fibrosis, cirrhosis, ALD	Dominant eicosanoid in cirrhosis, induces hepatic fibrosis via the TGF-β/Smad3 signaling; Promotes vasoconstriction and hypertension via the GPR75 pathway; Enhances hepatic steatosis and neutrophil infiltration in ALD	54,68,96–101

PG, prostaglandin; TX, thromboxane; COX-2, cyclooxygenase-2; I/R, ischemia-reperfusion; MCP-1, chemoattractant protein-1; PGES1, PGE_2 synthase 1; AD, acute decompensation; ACLF, acute-on-chronic liver failure; PDGF, platelet-derived growth factor; HSC, hepatic stellate cells; TGF-β, transforming growth factor-β; EP, prostaglandin E receptor; NASH, non-alcoholic steatohepatitis; APAP, acetaminophen; LX, lipoxin; LOX, lipoxygenase; HCC, hepatocellular carcinoma; MDSC, myeloid-derived suppressor cell; LT, leukotriene; NAFLD, non-alcoholic fatty liver disease; CYP450, cytochrome P450; ALD, alcohol-related liver disease; GPR, G protein-coupled receptor.

Interaction between oxylipins and liver immune cells

KCs, the resident macrophages in the liver, release PGs in response to LPS stimulation.[74,110,111] Compared to other macrophage populations, KCs are particularly active in producing PGE_2. The expressions of both COX-2 and PGES1 were induced in KCs within 3 to 24 hours post-LPS treatment.[112] Moreover, KCs have also been confirmed as the primary source of TXA_2.[113–115] The concentration of TXA_2 in the culture medium of KCs isolated from bile duct ligation (BDL) mice was significantly higher than that from normal mice.[73] The TXA_2 produced by KCs binds to thromboxane prostanoid (TP) receptors, which activates T cells and promotes immune cell infiltration.[116] Inhibiting the COX-2 activity of KCs results in reduced hepatic production of TXA_2,[36,113,114] which subsequently leads to the production of LTB_4 and the 15-epimer of LXA_4.[117] In addition, KCs from damaged livers, when treated with phorbol ester or calcium ionophore, produce more LTs than PGE_2.[118] The enzyme 5-LOX is highly expressed in KCs and HSCs.[119] Researchers found that KCs utilized 12-/15-LOX to produce LTs,[120] and they also produced immunosuppressive HETEs and HDEAs via 15-LOX when exposed to DAMP signals from apoptotic cells.[121]

Treatment with inhibitors of 5-LOX and its activating protein FLAP affects KC morphology and apoptosis, leading to KC depletion and reduction of liver inflammation.[122,123] Inhibiting LOX reduces the production of reactive oxygen species (ROS) by macrophages in response to liver injury.[124] Additionally, blocking the LTB_4 receptor inhibits the expression of EGF, VEGF, and VEGF receptors in macrophages and affects their recruitment and I/R-induced liver injury.[125] Furthermore, PGE_2 and TXA_2 have been shown to regulate the function of KCs. Specifically, PGE_2 was shown to inhibit IL-1, IL-6, and ROS production by KCs in a dose-dependent manner.[16,126,127] Deficiency of TP receptor (activated by TXA_2) reduced pro-inflammatory gene expression and cytokine secretion in KCs stimulated by TNF-α, H_2O_2, or PA.[128] Conversely, TXA_2 promoted KC activation in a TP receptor-dependent manner, thereby contributing to lipogenesis in primary hepatocytes and the development of NAFLD.[128]

Bioactive oxylipins critically regulate KC polarization dur-

ing liver disease progression. Cytokine-driven reprogramming governs macrophage differentiation into pro-inflammatory (M1) or anti-inflammatory (M2) states, with KCs predominantly adopting an M1 phenotype in injury contexts.[129,130] Crucially, transition to the M2 phenotype enables inflammation resolution and tissue regeneration—a process orchestrated by SPMs.[131,132] Notably, RvD1, a key member of the RvD family, significantly attenuates the I/R-induced changes in macrophages, inhibits the expression of IL-1β and IL-6, alleviates the M1 polarization state of KCs during liver injury, and promotes the resolution of inflammation.[131,133] This regulatory effect of RvD1 depends on the presence of KCs. Depletion of KCs using liposomal clodronate abolishes its impact on pro-inflammatory mediators and macrophage polarization.[131,133] Similarly, MaR1 has been demonstrated to enhance the expression and transcriptional activity of retinoic acid-related orphan receptor α, which is considered a key regulator of polarization in liver macrophages. This consequently results in an increase in the M2 polarization of KCs.[134] However, conflicting evidence suggests that spleen- and bone marrow-derived macrophages, rather than KCs, may serve as the primary source of SPMs.[135] Taken together, these findings indicate that various oxylipins can modulate macrophage function, with their effects intricately linked to the cellular context and specific subsets of macrophages involved.

Furthermore, while the interaction between oxylipins and liver macrophages is well-documented, recent research has also focused on the effects of oxylipins, particularly PGs, on other cell subgroups such as HSCs, T cells, and neutrophils.[105,106,127,136] For instance, PGE_2 is shown to dose-dependently drive neutrophilic inflammation resolution in the absence of macrophages in a zebrafish model.[137] Researchers have demonstrated that PGE_2 can increase the immunosuppressive potential of Treg cells and convert $CD4^+CD25^-$ T cells into an immunosuppressive phenotype by inducing FOXP3.[136,138] Moreover, studies have shown that senescent HSCs produce PGE_2 in NASH, which plays a pivotal role in suppressing antitumor immunity.[139] Concurrently, TXA_2 acts on T cells to trigger an immunosuppressive pathway that is dependent on the guanine exchange factor ARHGEF1, suppressing T cell receptor-driven kinase signaling, proliferation, and effector functions. This mechanism may create a permissive microenvironment conducive to hepatic metastasis.[140] Certain oxylipins exert their effects on liver cells through their respective known receptors and signaling pathways, with the corresponding functional outcomes illustrated in Figure 1B and C.

Impact of gut microbiota on oxylipin metabolism

The gut microbiota has been shown to modify host oxylipin metabolism, exerting a certain influence on inflammation and metabolic homeostasis.[141] For instance, *Bacteroides fragilis* has been shown to downregulate host pro-inflammatory oxylipins such as 15-oxoETE while increasing AA levels, which are associated with reduced hepatic lipid accumulation and inflammation.[142] While intestinal microbial imbalance is a well-recognized contributor to the occurrence and progression of ESLD through metabolic disorders and PAMP-induced inflammation, little is known about the potential impact on host oxylipin metabolism. Some recent studies have investigated the effect of gut microbiota dysbiosis on host oxylipin pathways. For instance, gut microbiota dysbiosis induced by antibiotics or obesogenic diets significantly altered plasma oxylipin profiles in rats, with specific bacterial taxa like Proteobacteria positively correlated with the pro-inflammatory oxylipin LTB_4, linking microbial imbalance to obesity-related inflammation.[143] Additionally, another study has shown that translocation of the microbial metabolite lipoteichoic acid may cause excess PGE_2 production via COX-2 activation, thereby contributing to HCC progression.[139] Microbial lysates from patients with spontaneous bacterial peritonitis significantly enhance TXB_2 secretion in both human and mouse KCs, highlighting a direct microbial influence on TX synthesis.[144] Collectively, these findings indicate that gut microbiota may be a pivotal regulator of oxylipin-driven inflammatory and metabolic processes. However, the causal relationships and detailed mechanisms through which specific gut microbial communities influence host oxylipin pathways remain largely unexplored. Future studies are warranted to investigate how individual bacterial strains or consortia interact with host enzymes (e.g., COX, LOX, and CYP450) to modulate oxylipin metabolism and to unravel the molecular links between the microbiome and oxylipin-mediated immune signaling in the progression of liver diseases. Such investigations are expected to map potential networks across the microbiota-oxylipin-liver axis, thereby facilitating the creation of a comprehensive mechanistic framework linking the gut microbiota, oxylipins, and liver disease.

Bioactive oxylipins as potential therapeutic targets in liver injury and liver failure

Bioactive oxylipins and their corresponding oxidases, COXs, LOXs, and CYP450 enzymes, have been considered potential therapeutic targets in the context of liver injury and liver failure due to their involvement in the progression or resolution of liver disease (Fig. 2). Inhibition of enzymes and their related metabolites has been shown to alleviate liver inflammation and associated complications such as steatosis and fibrosis. COX-derived PGE_2 plays a significant role in immunosuppression in AD patients, and its level is increased in ACLF patients.[86,145] Albumin binds to PGE_2 and reduces its bioavailability, which in turn increases circulating TNF-α levels, reduces monocyte anergy, thereby potentially lowering infection risk.[86] The COX-2 inhibitor JTE-522 has been demonstrated to effectively reduce fibrogenesis in both rat models of liver cirrhosis induced by a choline-deficient diet and in a model of liver fibrosis induced by TAA.[37,146] Additionally, other COX-2 inhibitors, including DFU, meloxicam, and celecoxib, have individually demonstrated the ability to decrease TAA-induced liver injury, reduce BDL-induced collagen accumulation, and attenuate hepatic fibrosis and cirrhosis caused by BDL, CCl_4, and TAA.[147–151] Genetic ablation or pharmacological inhibition of 5-LOX by targeted delivery of the inhibitor zileuton improved CCl_4- and methionine-choline-deficient diet-induced hepatic fibrosis and liver injury.[102] Furthermore, zileuton has been shown to reduce acetaminophen- and LPS-induced liver injury, delay disease progression in HFD-induced NAFLD, and inhibit tumor development in diethylnitrosamine-induced HCC.[152–155] Clinically, administration of meloxicam has been found to ameliorate hepatic fibrosis in pediatric patients with chronic liver disease.[156] As an independent protective factor, COX-2 inhibitors have been shown to significantly reduce the incidence of decompensated events in cirrhosis patients following post-transjugular intrahepatic portosystemic shunt placement, improve liver function, and maintain a favorable safety profile.[157] Additionally, while conventional non-steroidal anti-inflammatory drugs frequently induce renal failure in patients with DC—a key concern in cirrhosis management—short-term administration of the selective COX-2 inhibitor celecoxib has been demonstrated to be renally safe in cirrhotic patients with as-

cites.[158]

Moreover, some oxylipins have anti-inflammatory properties and are involved in the resolution of liver disease. Administration of LXA_4 reduces hepatic immune cell infiltration as well as systemic inflammatory cytokine levels, thus attenuating alcoholic steatohepatitis in both wild-type and 12/15-LOX-deficient mice.[159] Treatment with 14,15-EET protects HepG2 cells from PA-induced inflammation and oxidative stress, while genetic disruption of *Ephx2*, which encodes soluble epoxide hydrolase, restores EET levels and attenuates liver injury.[160] Notably, combined intervention with a high ω-3 fatty acid diet and administration of the selective s-EH inhibitor TPPU (1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea) has been validated to attenuate CCl_4-induced liver fibrosis.[161] Moreover, NASH is accompanied by suppressed CYP epoxygenase activity and reduced hepatic and circulating EET levels, while EET administration promotes liver regeneration.[162] Preclinical data have further indicated that EET depletion by CYP epoxygenase suppression promotes NAFLD development, and EET augmentation attenuates steatosis, NASH, and fibrosis.[160,163,164] Thus, specific eicosanoids, such as LXA_4, PGE_2, and EETs, demonstrate hepatoprotective properties and represent potential treatment options for mitigating NAFLD progression. Potential therapeutic targets based on oxylipin metabolism and their corresponding oxidases in liver disease were summarized in Figure 2B.

Future prospects

The pathogenesis of ESLD, encompassing AD and ACLF, is highly complex, with significant heterogeneity among patient populations. Current research on oxylipins in ESLD remains limited and is largely derived from European cohorts with DC.[58,59] Comprehensive lipidomic or metabolomic studies are still needed to portray oxylipin dysregulation in other ESLD cohorts, such as those with viral hepatitis. Although existing cohort studies suggest a strong correlation between bioactive lipids and disease severity and progression in AD-ACLF, key influencing factors, such as chronic hepatitis background, immune and metabolic status (e.g., obesity, diabetes), and acute insults (e.g., viral activation, infection, drug toxicity) that induce alterations in bioactive lipids, have not been fully explored. Future research requires more detailed clinical subgroup analyses to characterize the alterations in bioactive lipids in complex ESLD scenarios.

From a mechanistic perspective, current research into the interplay between oxylipins and the immune system in ESLD has predominantly focused on macrophages, with a notable lack of systematic studies on other crucial immune populations, including liver-resident T cell populations, granulocytes, and peripheral immune cells. Furthermore, the synthesis of carrier proteins, such as apolipoproteins and albumin, which are vital for oxylipin transport, is significantly impaired in ESLD. How this deficiency affects oxylipin-mediated systemic inflammation represents an important yet understudied area. Additionally, intestinal microbial dysbiosis is a key driver of ESLD progression, yet few studies have reported its impact on host oxylipin metabolism. Thus, future investigations are warranted to explore how specific microbial strains interact with host enzymes (e.g., COX, LOX) to modulate oxylipin biosynthesis, and to unravel the molecular mechanisms linking particular microbial taxa to oxylipin metabolism and immune signaling. Such efforts can lay the foundation for developing precision therapies for ESLD based on oxylipin and gut microbiota profiles.

Finally, due to analytical limitations, the study of a wide variety of bioactive lipids primarily relies on lipidomics methods using liquid chromatography-mass spectrometry techniques. While non-targeted omics approaches provide a comprehensive profile of lipids, the identification of lipid molecules is not sufficiently accurate. Conversely, targeted omics methods, which offer reliable qualitative and quantitative information, are limited to a few categories of lipids due to the constraints of the existing lipid molecular libraries. Therefore, the development of new lipid quantification and *in vivo* tracking methods is essential for advancing the systematic study of oxylipins in liver diseases.

Conclusions

While the immunoregulatory roles of oxylipins and their contributions to liver injury in ESLD are increasingly recognized, their cellular sources and precise mechanisms of action remain incompletely characterized. Significant challenges persist, including patient heterogeneity, insufficient mechanistic insight beyond macrophage-centric views, and technical limitations in lipidomic analyses. Future research must prioritize multi-cohort validation, detailed clinical subtyping, expanded immune cell analyses, and the integration of host–microbe metabolic interactions. Overcoming these hurdles will be essential for developing oxylipin-based therapeutic and preventive strategies for ESLD.

Funding

This work was supported by the National Key Research and Development Program (2022YFA1303801, 2023YFC2506004), the National Natural Science Foundation of China (82370612, 32270853, U20A200603), the Zhejiang Provincial Natural Science Foundation of China (TGC24C050004), the Independent Project Fund of the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases (zz202312, zz202311), the Fundamental Research Funds for the Central Universities (2025ZFJH03), the Shandong Provincial Laboratory Project (SYS202202), and the Research Project of Jinan Microecological Biomedicine Shandong Laboratory (JNL-2025002B). The funders had no role in study design, data collection, or analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

YS has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication.

Author contributions

Draft of the manuscript (XS), preparation of tables and figures (AY, ST, MZ, MH, TL), citations and references (MZ, XX, XY), correction and revision of the manuscript (XS, JS, YS, ZhS, HB, ZeS). All authors have edited and approved the manuscript.

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