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Review

Oxylipin transport by lipoprotein particles and its functional implications for cardiometabolic and neurological disorders

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ABSTRACT

Lipoprotein metabolism is critical to inflammation. While the periphery and central nervous system (CNS) have separate yet connected lipoprotein systems, impaired lipoprotein metabolism is implicated in both cardiometabolic and neurological disorders. Despite the substantial investigation into the composition, structure and function of lipoproteins, the lipoprotein oxylipin profiles, their influence on lipoprotein functions, and their potential biological implications are unclear. Lipoproteins carry most of the circulating oxylipins. Importantly, lipoprotein-mediated oxylipin transport allows for endocrine signaling by these lipid mediators, long considered to have only autocrine and paracrine functions. Alterations in plasma lipoprotein oxylipin composition can directly impact inflammatory responses of lipoprotein metabolizing cells. Similar investigations of CNS lipoprotein oxylipins are non-existent to date. However, as APOE4 is associated with Alzheimer's disease-related microglia dysfunction and oxylipin dysregulation, ApoE4-dependent lipoprotein oxylipin modulation in neurological pathologies is suggested. Such investigations are crucial to bridge knowledge gaps linking oxylipin- and lipoprotein-related disorders in both periphery and CNS. Here, after providing a summary of existent literatures on lipoprotein oxylipin analysis methods, we emphasize the importance of lipoproteins in oxylipin transport and argue that understanding the compartmentalization and distribution of lipoprotein oxylipins may fundamentally alter our consideration of the roles of lipoprotein in cardiometabolic and neurological disorders.

1. Introduction

Biologically active oxygenated products of polyunsaturated fatty acids (PUFA), i.e., oxylipins, regulate many biological processes, including inflammation [1,2], energy metabolism [3–5], cell proliferation [6], differentiation [7] and senescence [8]. Throughout the animal kingdom, four primary routes of oxylipin generation occur, which include 1) lipoxygenases (LOXs), yielding fatty acid hydroperoxides leading to various downstream products, including hydroxy and keto fatty acids and numerous enzymatic rearrangements and secondary products, such as leukotrienes, lipoxins, resolvins and maresins [9,10]; 2) cyclooxygenases (COXs), producing prostaglandins and thromboxanes [11]; 3) cytochrome P450s (CYPs) responsible for the generation of omega-hydroxy and epoxy fatty acid leading to the epoxide hydrolase (EH)-dependent dihydroxy metabolites [12]; and 4) enzyme and/or autoxidation initiated reactive oxygen species (ROS)-mediated formation of fatty acid peroxides, and their respective rearrangement products including isoprostanes, isofurans and hydroxy fatty acids [13–15].

Since the discovery of prostaglandins in seminal fluid in the 1930s [16,17], the study of these and other oxylipins has been both extensive and fruitful, where oxylipins are found to be key players in both typical and pathophysiological conditions. Alterations in oxylipin metabolism have been identified in many inflammation-related disorders and diseases, including cancer [18], type 2 diabetes [19], metabolic syndrome [20,21], cardiovascular disease (CVD) [22,23], coronavirus disease (COVID)-19 [24–26], spontaneous preterm birth [27,28] and

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Alzheimer's disease (AD) [29]. Early studies identified free oxylipins as active agents, and the study of free oxylipins dominates the literature to date [30]. However, oxylipins, like their precursor fatty acids, are also incorporated into complex lipids, including phospholipids, cholesterol esters and triglycerides [31–37] and in plasma the majority are esterified within lipoprotein particles [32]. While the free oxylipins are clearly important in inflammation [2,17,38], the composition and roles of the esterified oxylipins are poorly understood, despite impaired lipoprotein metabolism being implicated in several inflammation-related diseases, such as atherosclerosis [39,40], COVID-19 [41,42], AD and AD-related dementia [43,44]. Meanwhile, evidence has emerged that acyl oxylipins can also elicit biological responses, or at least serve as a ready-to-access storage and transport reservoir for bioactive oxylipins [45–47]. Importantly, the interaction of immune cells and lipoproteins, which plays an impotent role in immunity adaptation [48,49], involves the exchange of esterified lipids [50,51]. Recent findings have pointed out the involvement of esterified oxylipins in immune tolerance [52], as well as the involvement of free oxylipins in trained immunity [53–55]. These findings suggest that a closer interrogation on the importance of esterified oxylipins in immune regulation, especially the regulation across the periphery and the brain, are warranted [56].

The functional role of lipoproteins for signaling molecule delivery to tissues has been well established over the past 2 decades, including roles for ceramides and sphingolipids in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) functions [57–60]. As considerable quantities of oxylipins are transported in esterified forms in lipoproteins [21,31,32], their impact on lipoprotein-metabolizing tissues also merits attention. For example, in plasma, over 90% of oxylipins are esterified into complex lipids, with the reminder in the non-esterified pool either within particles or adsorbed to circulating proteins [31,32]. Notably, density and size fractionation of lipoproteins yields particles with unique lipid mediator profiles that can be manipulated by both dietary patterns and health status [21,61,62]. Moreover, changes in lipoprotein oxylipin profiles can modulate the inflammatory responses of exposed cells [34,61]. The current review consolidates what is currently known regarding the methodologies of lipoprotein oxylipin analysis, the dietary patterns- and health status-specific composition and regulation of lipoprotein oxylipins, followed by the impact of lipoprotein oxylipin payloads on lipoprotein-metabolizing cells. The importance of lipoprotein oxylipins is emphasized by their implications on cardiometabolic and neurological disorders in the periphery and CNS. The current review therefore proposes that oxylipin transport via lipoproteins provides an endocrine mechanism of intercellular communication that may have important roles both in the periphery and in the CNS.

2. A brief review on the isolation, extraction, and analysis of lipoprotein oxylipins

Prior to exploring the biological significances of oxylipin transport by lipoproteins, it is important to consider the methods currently available for lipoprotein isolation and oxylipins quantification within those isolates, as it reveals key considerations for data interpretation, while highlighting innovation opportunities associated with technological knowledge gaps.

2.1. Lipoprotein particle isolation

Lipoprotein particle isolations have been reported using sequential flotation ultracentrifugation (SF-UC) classically using NaCl/KBr step gradients [63], size exclusion chromatography (SEC) [64], semi-preparative asymmetric flow field-flow fractionation (SP-AF4) [65], affinity chromatography [66], or hybrid approaches mixing techniques [62,67,68]. SF-UC is most often used as it allows for the isolation of large quantities of lipoproteins. This technique separates lipoprotein based on density in a scalable manner, but its relatively lengthy separation time, high shear forces, and use of high salt concentration may damage the structures and composition of lipoproteins [63,69–74]. In contrast, SEC, SP-AF4 and AF separations generally have lower capacity but are gentler and faster than SF-UC methods, with plasma samples maintained in near physiologic conditions during separation by size or protein specific interactions [65,69]. With proper care such as addition of antioxidant, usage of chelating agents as well as temperature control, and purging buffers/solvents with inert gases, even with SF-UC the level of lipid oxidation can be minimized, but the full extent of such protections are not clear [63].

A consideration for all isolation techniques is a preference for previously unfrozen samples, as one study pointed out the freezing at −80 °C (2 h) and thawing on ice (30 min) before SF-UC separation significantly changed the lipid composition, such as cholesterol, cholesterol ester, phospholipids and acylglycerols in lipoproteins [75]. When samples are handled in a uniform fashion, meaningful differences between study groups on lipoprotein oxylipins can be observed in previously frozen samples, but until studies are performed that empirically determine the effect size of freeze-thaw dependent changes, such impacts should be acknowledged and considered when interpreting study results.

To our knowledge, oxylipin determinations have only been reported with SF-UC using NaCl/KBr step gradients and SEC isolates using Superose™ 6 columns from GE Healthcare to date. Both Superose™ 6 and/or Superdex 200 SEC columns are often used for lipoprotein particle isolation [69,70,76,77]. Such a system is useful to separate lipoproteins of various sizes, but as with density, particles with different natures may overlap by size [69,78]. For instance, using the classic Superose 6 columns, HDL and albumin are only partially resolved [69,78]. The use of Superdex 200 columns can yield clean HDL fractions but result in significant overlap of very-low-density lipoprotein (VLDL) and LDL fractions. The HDL/albumin overlap using Superose 6 separation is likely to have a larger effect on non-esterified oxylipins than on esterified oxylipins within that pool, as albumin acts as a fatty acid binding protein with seven moderate-to-high-affinity binding sites (reviewed in [79]). Albumin binding of non-esterified oxylipins is likely, and it is likely to supersede levels in HDL, however their distribution between these pools remains unknown [78,80]. Lipoproteins are the major transporters of esterified lipids [81–86], and most circulating oxylipins exist in esterified forms [31,32]. While albumin can bind lysophospholipids and acylglycerols [80,87], such binding is limited to their structural similarity to free fatty acids and therefore less efficient compared to free fatty acids [86]. Moreover, these lipid classes are only minor components of HDL where 30–70% of the mass is lipid and dominated by phosphatidylcholines, cholesteryl esters, triacylglycerides, steroids and sphingomyelins [88,89]. Therefore, the impact of albumin contaminated HDL on HDL esterified oxylipin profiling efforts are likely limited. Moreover, the compartmentation of albumin and HDL is well distinguished from other lipoproteins such as LDL and VLDL, which has important biological implication mentioned later in the present review.

Recently, by coupling Sepharose 6 and Superdex 200 Increase columns, we have substantially enhanced chromatographic separations of particles, at the expense of extended processing times from 60 to 120 min (Fig. 1). Since functional and structural variations in sub-particles exist, and particle subclassifications varies by characterization/separation technique [90], higher resolution in particle separations is expected to provide a more nuanced view of the system being interrogated. Unfortunately, current techniques do not allow for the direct SEC-MS/MS, and high-resolution SEC analyses will ultimately require the analysis of large numbers of collected fractions for every sample processed, increasing the burden and cost of these analyses.

For research interested in oxylipin in extracellular vesicles (EVs), a technical challenge is the separation of lipoproteins and extracellular vesicles (EVs), as EVs has the similar size as LDL/VLDL and the similar density as HDL [91], and both lipoproteins and EVs are carriers of oxylipins [76,92]. However, both the particle concentration (with the estimated magnitude of $>10^7$ times in differences [91]) and lipid

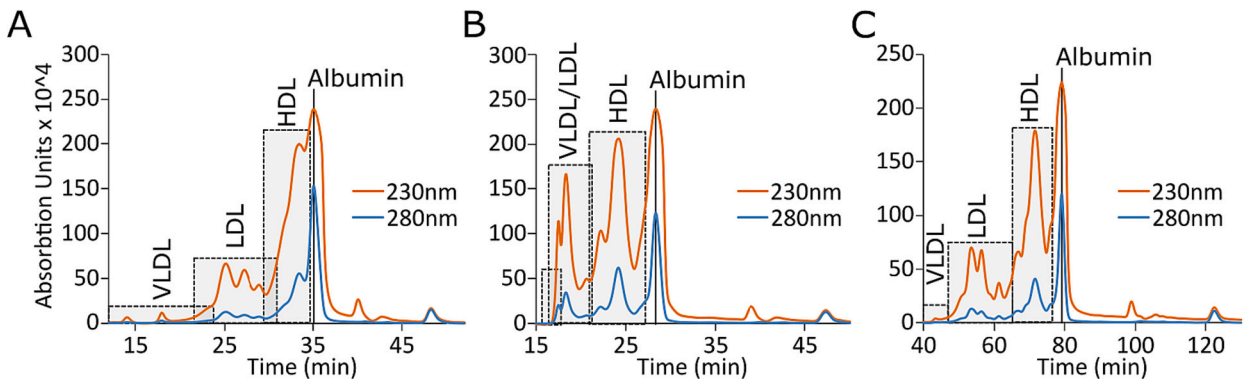

Fig. 1. Size exclusion chromatography of 35 μL of healthy human plasma using different column configurations. A) Superose 6 Increase; B) 10 × 300 cm Superdex 200 Increase; C) tandem 10 × 300 cm Superose 6 Increase and Superdex 200 Increase columns (GE Health Care). The apolipoprotein contents within these systems remains to be confirmed. Data are not published.

contents (with the magnitude of >8 times in differences [93]) of EVs are much less abundant compared to lipoproteins in human blood samples. The lower lipid content of EVs compared to lipoprotein reflects the nature of EV where a hydrophilic core is present and the nature of lipoprotein with a lipidic core [91,93]. Therefore, though a further improved method is encouraged, the commonly used SF-UC and/or SEC method for lipoprotein separation should be sufficient to discuss the biological relevance of lipoprotein oxylipins, but it will require the use of hybrid SF-UC/SEC, AF or novel technologies to allow careful examination of endogenous EV oxylipins as well as studies with interest in more hydrophilic compounds such as proteins and miRNA [92,94].

2.2. Lipoprotein oxylipin quantification

Approaches and pitfalls to MS-based oxylipin profiling have been extensively reviewed elsewhere [95]. In general, free oxylipins within separated lipoprotein fractions can be extracted directly with organic solvent prior to UPLC-MS/MS-MRM analysis as described in detail [34,96], while esterified oxylipins can be extracted and released by alkaline hydrolysis [97,98]. Solid phase extraction (SPE) clean-up procedures are then used to concentrate and purify extracts prior to the LC-MS/MS analysis of free oxylipin [19,96,97]. Factors affecting the recovery of oxylipins, such as stability of oxylipins during hydrolysis and potential sample loss due to liquid transferring, can be corrected by the usage of surrogates composite of deuterated oxylipins with similar chemical structures added to the total lipid extract prior to hydrolysis [99]. Currently, isotopically labeled oxylipins esterified in complex lipids are not commercially available, and such materials would greatly benefit the field. After alkaline hydrolysis and SPE clean-up, oxylipins such as alcohols, diols, triols, and epoxides can be reliably measured with surrogate correction [32,98,100], but many prostaglandin, ketone-prostaglandin and leukotrienes are completely degraded during hydrolysis [100–102]. This methodology therefore provides comprehensive and sensitive quantification of alkaline-stable esterified oxylipins, which covers a wide arrange of chemical structures relevant for the LOX, COX, CYP, sEH and nonenzymatic oxylipin pathways. Moreover, an international round robin exercise has demonstrated that this approach is reproducible if appropriate care is taken [103]. Alternatively, enzymatic hydrolysis of oxylipins can be performed prior to analysis, however such approaches will be subject to variability in substrate specificity of the enzyme used, which could have both advantages and disadvantages.

Another line of work uses LC-MS/MS to directly quantify the esterified oxylipins without hydrolysis [104]. Currently, less commercial analytical standards are available for esterified oxylipins compared to non-esterified oxylipins, so this quantification mainly relies on 1) in-house production and purification of analytical standards [105], 2) in silico prediction [106,107] and/or 3) semi-quantitative analysis using external standards of similar structures [108,109]. Direct quantification of esterified oxylipins without hydrolysis offers advantages such as shorter sample preparation time and the potential for imaging mass spectrometry [110,111]. Therefore, it is an important direction to advance our understanding on esterified oxylipin.

3. The presence of oxylipins in lipoproteins

3.1. The differential profile of lipoprotein esterified oxylipins and non-esterified oxylipins in plasma

In plasma, ~90% of oxylipins are present in esterified lipids, which are transported by lipoproteins [31,32], such as VLDL, LDL and HDL; meanwhile, there are both esterified and free, non-esterified oxylipin present within lipoprotein particles [34,78]. A previous study (Clinical Trial No. NCT00286234) inspected plasma oxylipins while investigating the impact of pharmaceutical grade omega-3 fatty acid supplementation (P-OM3) and niacin on insulin-resistance [21]. By comparing the oxylipin compositions in the plasma non-esterified and lipoprotein-esterified pools from healthy controls, it becomes clear that plasma sub-compartments are compositionally unique (Fig. 2 and Table 1-2). Compared to VLDL and LDL, the HDL fraction is enriched in 20 to 22 carbon (i.e. C20-C22) polyunsaturated oxylipins, consistent with the higher phospholipid content of HDL compared to other lipoproteins [112]. As particle density decreases, HDL > LDL > VLDL, triglyceride content increases [112], accompanied an increase in eighteen carbon (i.e. C18) oxylipins as a percentage of the total oxylipin pools (Table 1). Free oxylipins have the same percentage level of C18 and C20–22 oxylipins compared to LDL. Mid-chain alcohols dominate the oxylipin profile of all particles in this healthy cohort (Fig. 2); similar trends are also reported in rats [99].

It should be emphasized that such results were reported as the percentage composition of oxylipins in each lipoprotein fraction, and the direct comparisons on the oxylipins distribution among different lipoproteins also requires the absolute quantitation of lipoproteins concentrations in these subjects. For such a comparison, a rodent study on healthy and nephrotic rats has indicated that HDL carries the majority of mid-chain alcohols (hydroxyeicosatetraenoic acids (HETEs) and hydroxyoctadecadienoic acids (HODEs)) in rats, while VLDL carries more epoxides and diols but only in nephrotic rats [99]. However, the same comparison is not yet available in human study.

3.2. The source of lipoprotein oxylipins

Oxylipins can be formed by oxygenation of precursor fatty acids or through the direct oxygenation of lipids within membranes. Therefore, multiple routes for their incorporation into lipoprotein particles exist.

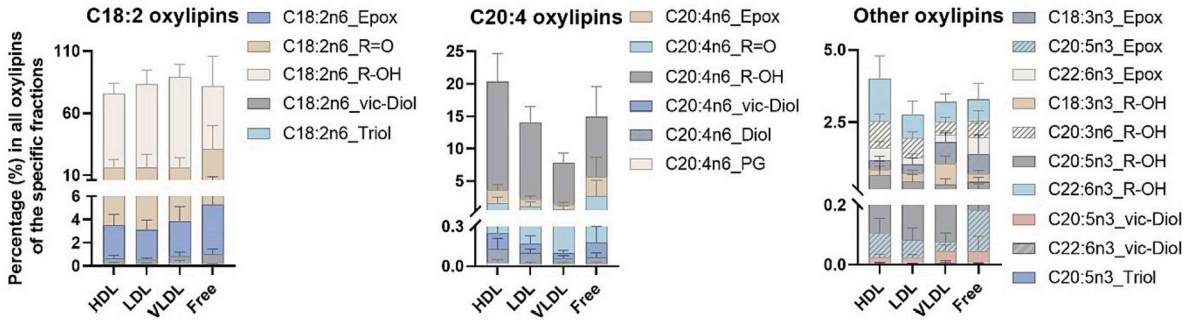

Fig. 2. Oxylipins percentage composition in HDL, LDL, VLDL and free plasma oxylipin fraction in human. Figure reproduced from the data of healthy participants (n = 14, aged 40–69) from a previous study [21]. Significant differences are indicated in Tables 1 and 2.

Table 1
C18 and C20–22 oxylipins concentration percentage composition (%) in HDL, LDL, VLDL and free oxylipin fraction in human plasma. Table reproduced from the data of healthy participate (n = 14, aged 40–69) from a previous study [21]. Tukey HSD post hoc analysis was done using the concentration percentage of oxylipin groups after Johnson normalization. Different letters indicate different significant levels of the same oxylipin group among different pools.

Fractions	C18 oxylipin (%)	Sig level	C20–22 oxylipin (%)	Sig level
HDL	76% ± 6%	C	24% ± 6%	A
LDL	84% ± 3%	B	16% ± 3%	B
VLDL	90% ± 2%	A	10% ± 2%	C
Free	83% ± 4%	B	17% ± 4%	B

The COX- and CYP-derived oxylipins are formed from free fatty acid, with substrate availability regulated by phospholipase A2 (PLA2) activation [113–117]. In contrast, LOX-derived oxylipin can be generated through both direct and indirect oxidation [47]. Specifically, the direct oxidation of cellular membrane unsaturated fatty acids can be stimulated by the calcium-dependent translocation of LOX and activation of their oxidase activity [118–120]. Conversely, LOX metabolism of non-esterified fatty acid can lead to the formation of non-esterified LOX oxylipins [121]. Notably, both CYP-derived epoxy and LOX-derived hydroxy fatty acids are substrates of long-chain acyl-coenzyme A synthases (ACSLs) [122], and can thus participate in the Land cycle, leading to their incorporation into phospholipid membranes [121,123–126].

In addition, different lipid pools may exchange oxylipins. For instance, cholesterol esters can be oxidized by LOX directly to generate oxylipins in the cholesterol pools, which are then hydrolyzed and re-incorporated into the phospholipid pool through the Land cycle [36]. Meanwhile, non-esterified oxylipins can be incorporated into cellular esterified lipids, and different incorporation levels occur depending on the oxylipin structures, cell types and growth conditions [33]. For example, free 12-HETE is incorporated into the triacylglycerol fraction in 7 times of the amount into phospholipid in human neutrophils [35], while free 14(15)-epoxyeicosatrienoate (EpETrE) is incorporated into the phospholipids fraction 2.4-fold of the amount into the neutral lipids of porcine aortic smooth muscle cells [37]. However, it is not clear how these incorporation preferences of oxylipins into different lipid classes affect or reflect the overall distribution of oxylipins in lipoproteins.

3.3. Lipoprotein-mediated oxylipin transport

The current consensus view of oxylipin production and transport pathways are outlined in Fig. 3. Oxylipins can be incorporated into lipoproteins during lipid transport (reviewed in [127–131]). In humans, VLDL and LDL are responsible for transporting triacylglycerol and cholesterol/cholesterol esters from liver to other tissues under the regulation by an array of enzymes (e.g., lipoprotein lipase (LPL), hepatic lipase, cholesteryl ester transfer protein (CETP) and cell surface receptors (e.g., LDL receptor (LDL-R), LDL-R related protein, scavenger receptor class B type I (SR-B1)). On the other hand, nascent HDL phospholipid disks released from the liver accumulate non-hepatic cholesterol and phospholipid from peripheral cells, which are then taken up by the liver (i.e., the process of reverse cholesterol transport, reviewed in [127–131]). In a tracer study of perfused rat liver [97], oxylipins generated from deuterated free linoleic acid were incorporated into newly formed VLDL, where CYP derivatives (epoxy-octadecenoic acid, EpOMEs) were estimated to have a higher rate of incorporation than LOX derivatives (HODEs). This preference of epoxides over hydroxides does not explain the higher amount of HODEs compared to EpOMEs in VLDL, suggesting an additional regulation on the oxylipin profiles in rat liver. In the same study, VLDL oxylipins profile was altered by LPS stimuli of the liver, which also suggests the potential of VLDL oxylipin to reflect metabolic state of the liver. Since CYP [132] and LOX [133] oxylipin regulations are species-specific, the translation of such kinetic results from rodents to human are yet to confirm.

Macrophage, one of the essential components in inflammatory responses (reviewed in [134]), effluxes phospholipids and cholesterol to preβ-1-HDL to form nascent (immature) HDL via ATP-binding cassette transporter A1 (ABCA1) [50,127]. In addition, macrophages efflux cholesterol to mature HDL via ATP-binding cassette transporter G1 (ABCG1) and SR-B1 and to extracellular space via aqueous diffusion, which then get incorporated into HDL (reviewed in [127,135,136]). Our preliminary data has suggested the movement of esterified oxylipins from macrophage to ApoA1 protein is mediated by ABCA1 (Fig. 4). This finding indicates that machinery needed for the HDL trafficking of oxylipins from periphery exists. However, questions remain whether the inflammatory state of the periphery, for example due to low grade systemic inflammation, changes oxylipin composition in HDL and whether impaired HDL oxylipin efflux can influence peripheral inflammatory burden and modulate cardiometabolic risks. Similarly, ApoA1 can also directly bind free oxylipins, including both fatty acids hydroperoxides and alcohols, as well as oxidized phospholipids [137]. In contrast, ApoA1 cannot bind cholesterol and its oxidized derivatives [137]. Even though the binding of oxidized oxylipins is much weaker compared to the binding to free long-chain fatty acids [137], these findings suggest the potential role of ApoA1 and ApoA1-HDL in oxylipins clearance and by doing so – potentially modulating inflammation.

In addition to the incorporation of oxylipins into the lipoproteins, oxylipins profiles in lipoproteins can be altered by the direct modification of lipoproteins. LDL can be converted into oxidized LDL (oxLDL) by LOX [138], CYP [139] and other non-enzymatic oxidative reagents [140]. Oxylipins, both esterified [141] and non-esterified [142], are generated to various degrees during the formation of oxLDL. In non-enzymatic oxidation of LDL, the majority of the non-esterified oxylipins formed during the process switched from AA-derived oxylipins to the LA-derived oxylipins as the oxidation time progressed within 30 h [142]. Nonenzymatic formation of oxLDL also changes its content of isoprostanes (IsoP) and prostaglandins (PGs) [143]. Interestingly, while

Table 2
Oxylipins composition (%) in HDL, LDL, VLDL and free oxylipin fraction in human plasma. Table reproduced from the data of healthy participate (n = 14, aged 40–69) from a previous study [21]. Tukey HSD post hoc analysis was done using the percentage of oxylipins after Johnson normalization. Different letters indicate different significant levels of the same oxylipin among different pools.

				Percentage (%Average ± %Standard deviation)				Sig level*			
Chemical Class	Source	Parent FA	Oxylipins	HDL	LDL	VLDL	Free	HDL	LDL	VLDL	Free
Epox	CYP	C18:2n6	12(13)-EpOME	1.39 ± 0.424	1.22 ± 0.341	1.59 ± 0.701	2.22 ± 2.03	A	A	A	A
Epox	CYP	C18:2n6	9(10)-EpOME	1.43 ± 0.518	1.36 ± 0.495	1.45 ± 0.616	2.08 ± 1.53	A	A	A	A
Epox	CYP	C18:3n3	12(13)-EpODE	0.0131 ± 0.00784	0.0134 ± 0.00956	0.0563 ± 0.0297	0.0355 ± 0.0397	C	C	A	B
Epox	CYP	C18:3n3	15(16)-EpODE	0.142 ± 0.0751	0.151 ± 0.106	0.344 ± 0.162	0.344 ± 0.364	B	B	A	AB
Epox	CYP	C18:3n3	9(10)-EpODE	0.156 ± 0.0662	0.155 ± 0.0962	0.344 ± 0.133	0.312 ± 0.266	B	B	A	AB
Epox	CYP	C20:4n6	11(12)-EpETrE	0.947 ± 0.484	0.557 ± 0.204	0.346 ± 0.145	1.25 ± 1.19	A	A	B	A
Epox	CYP	C20:4n6	14(15)-EpETrE	0.628 ± 0.239	0.397 ± 0.153	0.276 ± 0.113	1.14 ± 1.28	A	AB	B	A
Epox	CYP	C20:4n6	8(9)-EpETrE	0.373 ± 0.16	0.228 ± 0.106	0.164 ± 0.0782	0.55 ± 0.515	A	AB	B	A
Epox	CYP	C20:5n3	17(18)-EpETE	0.0781 ± 0.0525	0.0558 ± 0.0377	0.0333 ± 0.0294	0.136 ± 0.187	A	AB	B	A
Epox	CYP	C22:6n3	16(17)-EpDPE	0.192 ± 0.0901	0.107 ± 0.0638	0.114 ± 0.0566	0.283 ± 0.255	AB	B	AB	A
Epox	CYP	C22:6n3	19(20)-EpDPE	0.229 ± 0.152	0.119 ± 0.0649	0.132 ± 0.0898	0.285 ± 0.238	A	A	A	A
vic-Diol	sEH	C18:2n6	12,13-DiHOME	0.0687 ± 0.0781	0.0461 ± 0.0269	0.0688 ± 0.0507	0.0817 ± 0.0894	A	A	A	A
vic-Diol	sEH	C18:2n6	9,10-DiHOME	0.416 ± 0.198	0.289 ± 0.112	0.476 ± 0.303	0.742 ± 0.397	AB	B	AB	A
vic-Diol	sEH	C20:4n6	11,12-DiHETrE	0.00697 ± 0.00393	0.00575 ± 0.00514	0.00265 ± 0.00166	0.0116 ± 0.0143	A	A	B	A
vic-Diol	sEH	C20:4n6	14,15-DiHETrE	0.00496 ± 0.00127	0.00405 ± 0.00188	0.00285 ± 0.00128	0.0066 ± 0.00436	A	AB	B	A
vic-Diol	sEH	C20:4n6	5,6-DiHETrE	0.0674 ± 0.0514	0.0457 ± 0.0416	0.0245 ± 0.0172	0.0689 ± 0.0735	A	AB	B	A
vic-Diol	sEH	C20:4n6	8,9-DiHETrE	0.0361 ± 0.037	0.0145 ± 0.0118	0.00778 ± 0.00414	0.0278 ± 0.027	A	BC	C	AB
vic-Diol	sEH	C20:5n3	14,15-DiHETE	0.00636 ± 0.00657	0.0063 ± 0.00635	0.00571 ± 0.00467	0.0118 ± 0.0137	A	A	A	A
vic-Diol	sEH	C20:5n3	17,18-DiHETE	0.0183 ± 0.00974	0.0114 ± 0.00613	0.0293 ± 0.0192	0.0275 ± 0.0354	AB	B	A	AB
vic-Diol	sEH	C22:6n3	19,20-DiHDPA	0.00162 ± 0.000852	0.000883 ± 0.000485	0.00167 ± 0.0013	0.00265 ± 0.00191	AB	B	AB	A
R = O	ADH	C18:2n6	13-KODE	10.1 ± 5.56	10.8 ± 9.41	10.1 ± 7.29	23.3 ± 18.4	AB	AB	B	A
R = O	ADH	C18:2n6	9-KODE	1.92 ± 0.684	1.94 ± 0.777	1.76 ± 0.548	1.88 ± 0.722	A	A	A	A
R = O	ADH	C18:2n6	EKODE	0.747 ± 0.749	0.6 ± 0.469	0.606 ± 0.203	0.664 ± 0.333	A	A	A	A
R = O	ADH	C20:4n6	15-KETE	1.05 ± 0.698	0.724 ± 0.676	0.435 ± 0.456	2.24 ± 2.16	A	AB	B	A
R = O	ADH	C20:4n6	5-KETE	0.387 ± 0.25	0.184 ± 0.097	0.117 ± 0.0902	0.337 ± 0.224	A	AB	B	A
R-OH	LOX	C18:2n6	13-HODE	47.4 ± 7.38	53.7 ± 9.44	58 ± 8.53	40.8 ± 19.7	B	AB	A	B
R-OH	LOX	C18:2n6	9-HODE	12 ± 1.66	13.1 ± 2.08	14.7 ± 1.99	9.81 ± 4.34	B	AB	A	B
R-OH	LOX	C18:3n3	13-HOTE	0.0922 ± 0.0535	0.109 ± 0.0485	0.306 ± 0.099	0.107 ± 0.0442	B	B	A	B
R-OH	LOX	C18:3n3	9-HOTE	0.121 ± 0.0478	0.166 ± 0.0635	0.424 ± 0.179	0.16 ± 0.0806	B	B	A	B
R-OH	LOX	C20:3n6	15(*S*)-HETrE	0.932 ± 0.236	0.666 ± 0.206	0.446 ± 0.137	0.568 ± 0.337	A	AB	B	B
R-OH	LOX	C20:4n6	12-HETE	2.34 ± 0.896	1.45 ± 0.279	0.801 ± 0.263	1.16 ± 0.586	A	B	C	BC
R-OH	LOX	C20:4n6	15-HETE	4.17 ± 0.824	2.96 ± 0.733	1.67 ± 0.411	2.44 ± 1.36	A	B	C	BC
R-OH	LOX	C20:4n6	5-HETE	3.11 ± 0.597	2.26 ± 0.447	1.22 ± 0.317	1.82 ± 0.789	A	B	C	B
R-OH	LOX	C20:4n6	8-HETE	1.88 ± 0.616	1.39 ± 0.344	0.768 ± 0.242	1.05 ± 0.545	A	AB	C	BC
R-OH	LOX	C20:5n3	12(*S*)-HEPE	0.211 ± 0.186	0.148 ± 0.0979	0.11 ± 0.0862	0.0957 ± 0.0683	A	A	A	A
R-OH	LOX	C20:5n3	15(*S*)-HEPE	0.12 ± 0.136	0.0824 ± 0.0743	0.0631 ± 0.0459	0.0568 ± 0.0289	A	A	A	A
R-OH	LOX	C20:5n3	5(*S*)-HEPE	0.237 ± 0.18	0.147 ± 0.0797	0.111 ± 0.0751	0.116 ± 0.0676	A	A	A	A
R-OH	LOX	C22:6n3	17(*R*)-HDoHE	1.47 ± 0.782	0.816 ± 0.445	0.689 ± 0.267	0.742 ± 0.546	A	AB	B	B
R-OH	COX	C20:4n6	11-HETE	2.32 ± 0.593	1.64 ± 0.371	0.898 ± 0.221	1.34 ± 0.715	A	B	C	BC
R-OH	Autoox	C20:4n6	9-HETE	2.89 ± 1.34	2.06 ± 0.869	1.05 ± 0.529	1.45 ± 0.972	A	AB	C	BC
Diol	LOX	C20:4n6	5,15-DiHETE	0.0197 ± 0.0176	0.0175 ± 0.00754	0.00772 ± 0.00582	0.0112 ± 0.00951	A	A	B	AB
Diol	LOX	C20:4n6	6-trans-LTB4	0.0148 ± 0.00627	0.0159 ± 0.00955	0.00481 ± 0.00504	0.00874 ± 0.0085	AB	A	C	BC
Diol	LOX	C20:4n6	8,15-DiHETE	0.0545 ± 0.0575	0.0385 ± 0.0134	0.0163 ± 0.00848	0.023 ± 0.0151	A	AB	C	BC
Diol	LOX	C20:4n6	LTB4	0.00725 ± 0.00259	0.00709 ± 0.0049	0.0124 ± 0.0123	0.00397 ± 0.00217	A	AB	A	B
Triol	LOX	C20:5n3	Resolvin E1	0.00417 ± 0.00408	0.00321 ± 0.00212	0.00535 ± 0.00866	0.00315 ± 0.00188	A	A	A	A
Triol	Autoox	C18:2n6	9,10–13-TriHOME	0.0884 ± 0.0363	0.0956 ± 0.0304	0.119 ± 0.0759	0.0765 ± 0.0172	A	A	A	A
Triol	Autoox	C18:2n6	9,12,13-TriHOME	0.129 ± 0.0621	0.136 ± 0.0289	0.17 ± 0.119	0.114 ± 0.0251	A	A	A	A
PG	COX	C20:4n6	PGF2a / (isoprostanes)	0.0326 ± 0.0161	0.0238 ± 0.00742	0.016 ± 0.00717	0.0213 ± 0.0131	A	AB	B	AB

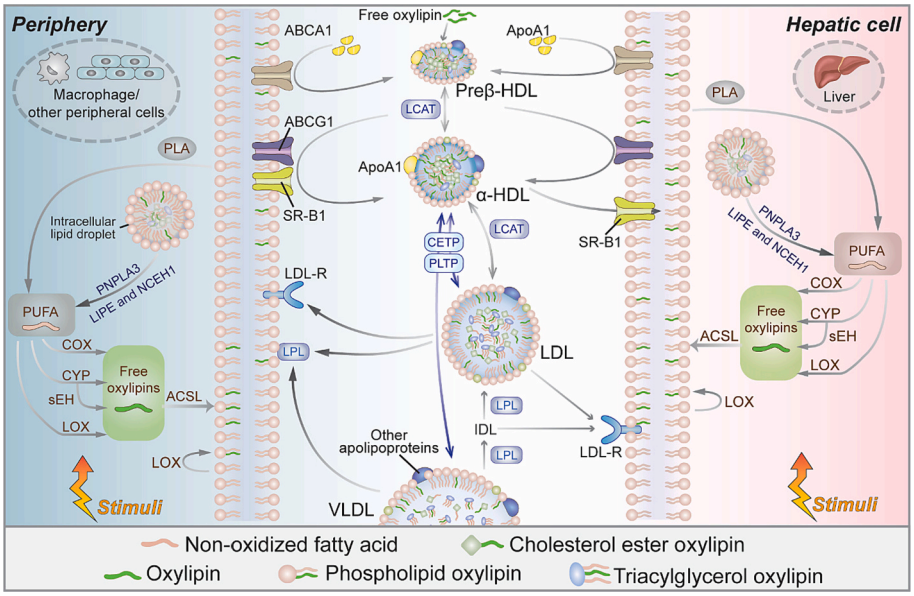

Fig. 3. Proposed overview of oxylipin production in cells and their transportation between cellular membranes and lipoproteins. Oxylipins are transported along lipid metabolizing pathways. The liver exports oxylipins to VLDL and subsequently LDL, with the composition reflecting the inflammatory state of the liver. Upon incorporation via LDL receptor (LDL-R), oxylipins in LDL can modify the inflammatory response of peripheral cells. Peripheral cells export oxylipins to ApoA1 or HDL through ABCA1 and ABCG1 complexes or SR-B1. HDL oxylipin composition reflects the inflammatory state of the periphery. Abbreviation: ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; ACSL: long-chain acyl-coenzyme A synthase; ApoA1: apolipoprotein A-1 (Apo-AI); CETP: cholesteryl ester transfer protein; COX: cyclooxygenase; CYP: cytochrome P450; HDL: high-density lipoprotein; LCAT: lecithin cholesterol acyl transferase; LIPE: lipase E, hormone sensitive type; LDL: low-density lipoprotein; LDL-R: low-density lipoprotein receptor; LOX: lipoxygenase; LPL: lipoprotein lipase; NCEH1: neutral cholesterol ester hydrolase 1; PLA: phospholipase; PLTP: phospholipid-transfer protein; PNPLA3: patatin-like phospholipase domain-containing protein 3; PUFA: polyunsaturated fatty acid; SR-B1: scavenger receptor class B type I; sEH: soluble epoxide hydrolase; VLDL: very-low-density lipoprotein.

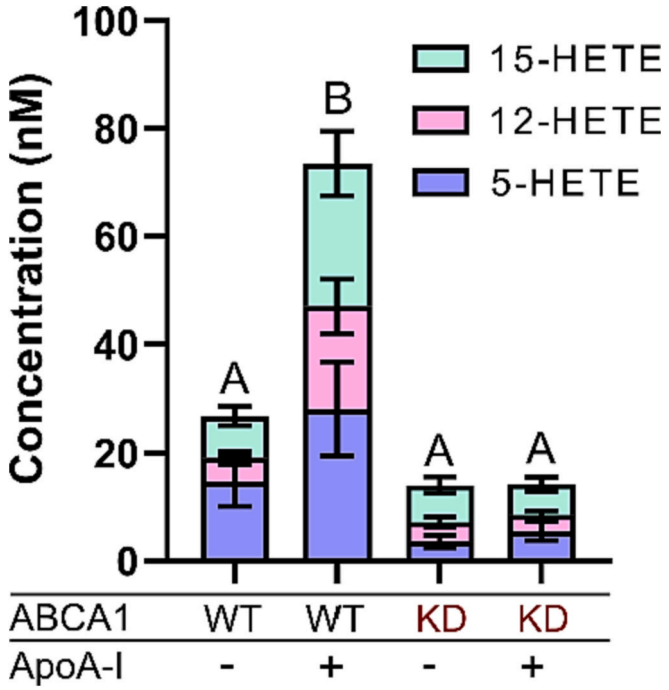

Fig. 4. ABCA1 mediated transfer of lipid mediators from macrophages to ApoA1 particle. Raw 264.7 macrophage (n = 3), wild type (WT) or ABCA1 knock down (KD) were treated with 100 ng/mL of LPS for 60 min and subsequently exposed to 40 μg/mL ApoA1. The graph shows concentration of esterified LOX metabolites of arachidonic acid in cell media. Error bars represent 95%CI. Data are not published.

CYP can modify LDL [139], oxLDL can in turn suppress the expression of CYP [144]. As a result of these modifications, the functions of lipoproteins can be changed, which will be considered in detail in the later section.

Other lipoprotein metabolism regulators may also modulate their oxylipin composition. For example, lecithin-cholesterol acyltransferase (LCAT) converts free cholesterol and phosphatidylcholine into cholesterol esters and lysophosphatidylcholine mainly during the process of HDL maturation (reviewed in [145]). CETP exchange cholesterol ester and triacylglycerol between HDL and other lipoproteins that contain ApoB (reviewed in [146,147]). Plasma phospholipid-transfer protein (PLTP) mediates the exchange of phospholipid and cholesterol between HDL and triacylglycerol-rich lipoproteins (reviewed in [148]). These regulations can potentially exchange oxylipins among lipoproteins, as well as incorporating oxylipins from cellular lipids into lipoproteins, which requires further investigation.

Furthermore, other elements regulating lipid homeostasis, such as liver X receptors (LXR) (reviewed in [149]), sterol response element binding protein 2 (SREBP-2) [150,151], other scavenger receptors (e.g. SR-A1 and CD36)(reviewed in [152,153]), patatin-like phospholipase domain-containing protein 3 (PNPL3) [154–156], lipase E, hormone sensitive type (LIPE) [157,158] and neutral cholesterol ester hydrolase 1 (NCEH1) [159] should be closely investigated in the context of oxylipin transport via lipoproteins as well as intracellular lipid droplets.

In summary, evidence has suggested that the oxylipins originated from oxylipin-producing cells can be incorporated into lipoproteins and participate in circulation. In addition, oxylipins can be formed by direct modification of lipoproteins. However, the detail fractionation and analysis of oxylipins in each lipoprotein particle, as well as the characterization of their trajectories across periphery, liver, brain, and other lipoprotein-metabolizing locations, are still largely unexplored.

4. The effect of lipoprotein oxylipins on lipoprotein-metabolizing cells

Esterified oxylipins are present in lipoproteins in non-pathological conditions [32], suggesting their availability to participate in homeostatic regulation. In contrast, modified lipoproteins, especially oxLDL, and their cellular functions has been investigated extensively due to their importance in vascular injury and inflammatory-related disorders (reviewed in [160]). The modification to convert LDL to oxLDL is an important process for their uptake by macrophages [51,161,162]. OxLDL can be taken up by macrophages and induces expression of specific inflammatory and oxidative stress biomarkers in macrophages [143]. However, the esterified oxylipins profile of oxLDL, as well as other modified lipoproteins, has only been linked to their functional characteristics to a very limited degree.

A few studies indeed demonstrated the critical composition-function relationship of lipoproteins oxylipins and lipoprotein-metabolizing cells. For example, one study utilized lipoproteins from subjects with pro- and anti-atherogenic phenotypes. The pro-atherogenic phenotype was defined by their triglyceride-rich lipoproteins (TGRL) ability to cause >10% increased expression of vascular cell adhesion molecule (VCAM)-1 in TNFα-treated human aortic endothelial cells (HAEC); the anti-atherogenic phenotype was defined by TGRL inducing >10% decreased expression VCAM-1 [34]. As results of a standard meal high in saturated fat, the postprandial TGRL from pro-atherogenic subjects further increased ~50% of the expression of VCAM-1 in TNFa-treated HAEC, while the one from anti-atherogenic subjects further decreased ~40% of this expression. Accordingly, the postprandial shift of oxylipin profile in TGRL, mainly the sEH-derived diols in esterified and non-esterified pools and non-esterified LOX-derived alcohols, were well discriminated between the pro- and anti-atherogenic subjects. Meanwhile, the oxylipin composition of TGRL predicted VCAM-1 expression in HAEC. Consistently, the representative oxylipins of the pro-atherogenic TGRL, methyl ester of 9-HODE and 12,13-DiHOME (analogues of their free oxylipin forms) reduced VCAM-1 expression in TNFa-treated HAEC, where the low abundance of these two oxylipins in the pro-atherogenic fasting TGRL was associated with the high VCAM expression. Another study has demonstrated a similar finding: after 4-weeks of 40 g/day dietary walnut intervention, plasma LDL from hypercholesterolemic, postmenopausal female subjects decreased inflammatory-related IL-8 and IL-6 production in the TNFα-stimulated primary human diabetic adipocytes [76]. Meanwhile, among the esterified oxylipins, the LDL from such dietary intervention had higher ALA and its epoxide contents, but lower levels of monounsaturated fatty acids and AA/DGLA-derived mid-chain alcohols. The esterified oxylipin composition of LDL was strongly correlated with the TNFα-stimulated cell secretion of IL-6 and IL-8, including negative association with ALA epoxides and positive association with AA/LA alcohols, but not their precursor fatty acids. These studies indicated that the lipoprotein oxylipins can be well correlated with the level of cellular inflammatory response. The evidence here also suggested LDL oxylipins are not only the products of an anti−/pro-inflammatory environment, but also a trigger for further inflammatory-related responses.

Altered oxylipin profiles of HDL is as well associated with the alteration of its function, which may have implication for inflammation. For example, the HDL from patients with Type 2 diabetes (T2D) had increased free HETEs (5-HETE, 15-HETE, and 12-HETE) and HODEs (9-HODE and 13-HODE) compared to the healthy controls [78]. This accompanied a high HDL inflammatory index in the patient groups, which was measured as the effect of HDL on the LDL-triggered monocyte migration using a monocyte chemotactic activity (MCA) assay. The free oxylipin contents were significantly associated with the decreased HDL antioxidant activity in a cell-free assay. Similar relationship between increased free LOX oxylipins in HDL and the increased pro-inflammatory properties of HDL were reported in heart failure [163], active rheumatoid arthritis (RA) [164] and idiopathic inflammatory myopathies [165]. These studies suggested the important composition-function relationship of oxylipins in HDL. However, these studies are limited to free oxylipin contents; it is also not clear if the detection of these HDL oxylipins is due to HDL's removal of inflammatory-related compounds from cells and/or the in-situ production of oxylipins in HDL triggered by various types of modification [166]. As another example, 15-lipoxygenase-treated HDL3 increased the apoptotic effect of oxLDL on human primary coronary artery endothelial cells, where the native HDL3 can reduce this effect [167]. Though the oxylipin profile of HDL was not investigated in this study, the NF-κB pathway mediating this process is also regulated by the LOX-derived oxylipins such as 13S-HOTE, 13S-HODE and 15S-HEPE [168], and thus the involvement of oxylipins can be speculated. Therefore, a closer investigation on the oxylipins in HDL and its potential contribution on the inflammatory-related properties of HDL [169] is warranted.

The functional changes of lipoproteins with altered oxylipins are also strongly indicated by another line of work, where the formation and bioactivities of non-enzymatically and enzymatically oxidized phospholipids in cell membranes were extensively investigated [47]. Phospholipid-oxylipins are produced by immune cells in response to stimulation and participate in inflammation regulation [47,52,119,120]. Free oxylipins can function intracellularly (e.g. via nuclear receptors (peroxisome proliferator-activated receptors, PPAR) [170,171]) or extracellularly by interacting with cell membrane associated G protein–coupled receptor (GPCR) [170,172]; differently, esterified oxylipins in phospholipids are likely to remain associated with cellular membranes [120] prior to the action of PLA2 and the release of oxylipins from phospholipids. They are likely to mediate inflammatory environments by altering the structures of the membrane and thus the functions of membrane-associated proteins [47,52,173]. In particular, phospholipid-esterified oxylipin 15-HETE-phosphatidylethanolamine (PE) is a structural analog to the pro-inflammatory LPS and therefore compete with LPS to bind toll-like receptor 4 (TLR4) [174]. Interestingly, the production of 12/15 LOX-derived phosphatidylethanolamine (PE) allows the clearance of apoptotic cells in noninflammatory (resident) macrophages and limits the uptake of apoptotic cells in the inflammatory monocytes [52]. Such regulation is critical to maintain the self-immunologic tolerance. Furthermore, phospholipid oxylipins have other functions that contributes to homeostasis, such as promoting coagulation [175] and regulating ferroptosis [176]. The studies in this area highlight the extensive involvement of esterified oxylipins in phospholipids within and beyond the scope of inflammation. Considering the phospholipid contents in lipoproteins [112], HDL in particular, as well as the frequent lipid exchanges between lipoproteins and cell membranes [127], these studies can be highly translatable to esterified oxylipins in lipoproteins, which emphasizes the need for further investigation.

Additionally, the release of oxylipins from VLDL via LPL [32] suggests the potential for endocrine nature of oxylipin regulations, in addition to its autocrine and paracrine functions [177]. The release of oxylipins from lipoproteins by LPL showed preferences on the oxylipin species: LPL released all species of mid-chain hydroxides from VLDL to certain degrees, but not all species of epoxides and diols, and no ketones [32]. However, there are limited data on the uptake and release of oxylipins from other lipoprotein particles.

The migratory nature of macrophages [178] as well as its production of oxylipin [55,179–181] further support the hypothesis of paracrine or endocrine functions of oxylipins in regulating immunity. The polarization of macrophage into the M1/M2 phenotypes results in pro- or anti-inflammatory properties (reviewed in [134]), a process accompanied by the production of distinguished oxylipins (reviewed in [55]). Both M1 and M2 macrophage produced 5-LOX products such as 5-HETE and LTB4 and COX products such as TXB2 and PGE2, but M2 was distinguished from M1 with the up-regulated 15-LOX-1 expression and high concentration of 15-LOX products under bacterial co-incubation, including 15-HETE, 5,15-dihydroxyeicosatetraenoic acid (DiHETE),

17-hydroxydocosahexaenoic acid (HDHA), Resolvin D5 (7,17-dihydroxydocosahexaenoic acid), and Maresin 1 (7,14-dihydroxydocosahexaenoic acid) [55,179–181]. Similarly, astrocyte, one of the neuroinflammation-responsible cells, was polarized into pro−/anti-inflammatory (A1/A2) phenotype under different stimuli (LPS, IL-4, and IL-10), and these phenotypes had different oxylipin profiles from each other; these oxylipin profiles also reflect their further inflammatory adaptation in response to a second stimuli [182]. These studies indicate that the oxylipin profiles may play a role in the inflammation regulation in these migrating immunologically important cells.

In addition, immune cells play a role in lipoprotein metabolism [127,183–185], and the interaction between these cells and lipoproteins, such as exposure of oxLDL to macrophages, is crucial in immune adaptation [48,49]. While the lipid transfer between these cells and lipoproteins is critical for their interaction [50,51], the direct involvement of lipoprotein oxylipins in these processes are unclear, despite that the involvement of esterified oxylipins in immune tolerance [52] and the involvement of free oxylipins in trained immunity [53–55,182] have been reported. Therefore, considering the composition of lipoprotein oxylipins is closely associated with the functions of lipoprotein-metabolizing cells [34,76,78], understanding how oxylipin exchanges occur between cells and lipoproteins is highly warranted. It will also be important to clarify if these oxylipin exchanges modifies the inflammatory characters of the cells and the lipoproteins, and whether these characters affect immunity adaptation processes, such as immune tolerance [52] and trained immunity [53–55]. Such investigations centering the role of lipoprotein oxylipins will provide deeper insight into the functions of these inflammatory cells and the involvement of impaired lipoprotein metabolism in inflammatory disorders across the periphery and the CNS [56].

In summary, the lipoprotein functionality is closely associated with their oxylipin composition [34,76,78]. Evidence has suggested that lipoprotein oxylipins are not only the products of inflammatory-related stimulus, but also triggers for further inflammatory-related responses [76]. Furthermore, the involvement of lipoprotein oxylipins in paracrine or endocrine functions have been indicated by their regulation via LPL and migrating immunologically important cells [32,134,182]. Their direct participation in various aspects of immunity warrants further investigation. [52–55,182]

5. Lipoprotein oxylipins in lipoprotein-associated disorders

5.1. Interplay between cardiometabolic disorders and oxylipin composition of lipoproteins

Evidence suggests that oxylipins in lipoproteins can influence inflammatory-related responses in cells, supporting an interplay between the inflammatory environment of cardiometabolic disorders and shifts in lipoprotein oxylipin profiles [34,76]. Moreover, the oxylipin composition of plasma lipoproteins reflect changes in metabolic status. For example, metabolic syndrome (MetSyn) is a metabolic state characterized by abdominal obesity, high triglycerides, high blood pressure, high fasting glucose, and low HDL-cholesterol. MetSyn uniquely changed oxylipin composition of all lipoprotein fractions. For example, HDL was reportedly increased most in mid-chain alcohols (LOX and autooxidation products) from DGLA and AA; LDL was increased in diols (sEH metabolites) and ketones from AA; VLDL has increased in the precursor fatty acids but most oxylipins, regardless of their precursors, were decreased, while AA-derived oxylipins were largely unchanged and LA and AA-ketones increased [21]. This may reflect the differential trafficking of oxylipins via various lipoproteins within a pro-inflammatory environment associated with this disorder. Such differential trafficking of pro- and anti-inflammatory oxylipins in lipoproteins has also been reported in a nephrotic rodent model, where HODEs and HETEs were increased in VLDL and HDL but decreased in LDL [99].

Accordingly, external stimuli such as dietary patterns can alter both cardiometabolic status and change peripheral lipoprotein oxylipins. Oxylipins are derived from polyunsaturated fatty acids and thus the oxylipin composition within lipoproteins generally reflects the dietary patterns induced changes in fatty acids composition [76]. Sixteen-week of prescription omega-3 fatty acids ethyl esters (P-OM3, 4 g/day) intervention resulted in reduced triglycerides and VLDL-C in serum, as well as reduced heart rate for MetSyn patients [21]. These changes were accompanied by reduced n-6 oxylipins and increased n-3 oxylipins to varying degrees in each lipoprotein, with substantially less n-6 oxylipin reduction in VLDL compared to HDL and LDL [21]. Interestingly, the changes in precursor fatty acids in lipoprotein didn't correlate with their oxylipins, suggesting regulation of oxylipin production beyond precursor fatty acid availability. Another study investigated the effect of dietary walnuts supplements (40 g/day, 4 weeks), a food source of high omega-3 ALA, on the plasma lipoprotein oxylipins in hypercholesterolemic, postmenopausal female subjects [76]. As a result of the dietary supplements, there were differential changes in oxylipins across lipoproteins. For example, several CYP-epoxides increased in HDL but showed decrease trends in LDL and VLDL. Meanwhile, across all lipoproteins, there was a preferential increase in ALA metabolites only in the CYP pathway but not the LOX pathway. On the contrary, all LOX and autoxidation oxylipins derived from other precursor fatty acids were reduced, possibly due to the polyphenol content of walnuts, serving as antioxidant and/or LOX inhibitors. These changes in lipoprotein oxylipins by dietary walnut intervention were accompanied by the improvement of microvascular functions associated with enrichment in HDL epoxy fatty acids [186]. These studies have emphasized the potential roles of lipoprotein oxylipins in mediating the relationship between inflammatory status and dietary intervention in the context of cardiometabolic disorders. Even more, the fractionation of lipoproteins unmasks the differential changes in oxylipins, which may also have biological implication in these disorders.

5.2. New area of interest: oxylipin's involvement in neurological disorders under the mediation of lipoproteins—indications and future prospective

Recent studies have linked the peripheral systemic metabolic dysregulation to the central pathologies across blood-brain/CSF barriers in neurological disorders, such as AD [187] and Parkinson's disease (PD) [188,189], as well as mental health disorders such as major depression [190] and Schizophrenia [191]. Meanwhile, the biosynthesis of the key components for the circulating lipoprotein metabolism are dysregulated in those neurological disorders, such as fatty acids, phospholipids, cholesterol, and apolipoproteins (reviewed in [44,192–195]). In light of the recently reported association between neurological disease risks and esterified/non-esterified oxylipins [196–199], we argue in the following sessions that oxylipins are likely to play its important role in neurological diseases under the mediation of lipoprotein metabolism, and thus it's crucial to interrogate the composition and functions of lipoprotein oxylipins in the context of neurological disorders, such as neurodegenerative diseases and infectious diseases that cause both peripheral and CNS symptoms.

5.2.1. The interplay between oxylipins and apolipoproteins/lipoproteins: an important target to understand neurodegeneration

Similar to cardiometabolic disorder, the development and progression of neurodegenerative diseases are often accompanied by the dysregulation in inflammation [200,201] as well as alternation of oxylipin profiles [196,197]. For example, compared to the healthy controls, the plasma free oxylipin profile in AD subjects indicate the upregulation of CYP450/sEH pathways and the downregulation of fatty acid ethanolamine pathway [196]. Consistently, plasma sEH metabolites (i.e., dihydroxy oxylipins) were associated with the lower perceptual speed in elderly subjects [198]. Meanwhile, AD associated lower fatty acids ethanolamides were also observed in cerebrospinal fluid (CSF), and CSF EpOMEs were associated with better cognitive performance in AD

subjects [196]. AD-associated changes are also reflected on the LOX pathways both in periphery and CNS: in the same study, several plasma LOX oxylipins decreased in AD patients compared to the healthy controls [196]. In certain affected areas of the AD post-mortem brain, LOX [202] and COX pathways [203,204] were upregulated. In contrast to these patterns of oxylipins between periphery and CNS, the non-esterified oxylipins in plasma and CSF are not well correlated to each other [196], and it remains unclear for esterified oxylipins between plasma and CSF. Therefore, questions remain on the precise nature of the oxylipin regulations across periphery and CNS, under normal and neurodegenerative pathologies.

Meanwhile, lipoprotein profiles and metabolism are associated with the risk for neurodegeneration [43,205,206]. Most importantly, the major genetic risk factor of neurodegeneration, the APOE4 gene, encodes an isoform of the ApoE apolipoprotein (ApoE4) critically involved in lipid trafficking and lipoprotein formation [193–195]. Compared to other isoforms, the expression of ApoE4 apolipoprotein increases neuronal amyloid beta (Aβ) synthesis [207], and the ApoE4 lipoprotein reduces the microglial efficiency to uptake Aβ and the capacity to improve Aβ's detrimental effect on cognition [208]. APOE4 is also associated with increased tau pathologies [209] and the leakage of blood-brain barrier [210]. Very interestingly, the prone-to-aggregation lipid-poor ApoE4 protein causes poor recycling of ABCA1 from late-endosomes to cell membrane, resulting in poor ABCA1 functions of lipid efflux [211]. Furthermore, APOE4 caused lipid profile changes in astrocytes, including increased level of unsaturation in fatty acids, intracellular triacylglycerol level and the storage of lipid droplets [212]. Meanwhile, apolipoprotein E4 alone also has the least protective effect on cells against oxidative stress [213] and the lower activity to inhibit Cu^{2+}-induced LDL oxidation [214], compared to other isoforms. Accordingly, the association between the APOE4 genotype and the high oxLDL level was observed in human studies [215]. Additionally, APOE also interacts with another risk factor for neurodegeneration [216] and microglia inflammatory regulator [217], triggering receptor expressed on myeloid cells 2 (TREM2) in a APOE isoform-specific manner [208]. Both TREM2 and APOE are critical for the barrier functions of microglia around the amyloid plague [218,219], where TREM2-apolipoprotein/lipoprotein binding is essential for the microglia's uptake of the complex of lipoproteins and β-amyloid peptide (Aβ) [220].

Recent studies have drawn connections between the regulation of oxylipins and APOE4 in neurodegeneration. Free oxylipins analysis on human post-mortem dorsolateral prefrontal cortex revealed that APOE3/4 carriers, compared to APOE3/3, had oxylipin profiles that correlated more strongly to cognitive functions and AD pathologies [199]. In the same study, when modeling the cognitive and pathological outcomes, the APOE genotypes have significant interaction with the amount of omega-3 fatty acids and several oxylipins, including prostaglandins, lipoxins, neuroprotectin D1 (NPD1) and 12-hydroxyheptadecatrienoic acid (12-HHT); however, in this study, the APOE genotypes didn't seem to alter sEH activities, measured as the product-precursor ratio in the sEH pathways, indicating that the APOE4-speicifc changes in oxylipins are enzyme-specific [199]. In addition, another study in periphery indicated that APOE isoforms altered oxylipin profile [221]: in this double-blinded, parallel randomized controlled trial of omega-3 fatty acids (in their triglyceride form) dietary intervention, the plasma hydroxy and dihydroxy oxylipins of EPA and DHA were increased in the APOE4 carriers compared to the APOE3 carriers after 12 months of supplementation of EPA and DHA [221]. Though not yet investigated, such isoform-specific dietary lipid regulation by APOE may have implications in the CNS, suggested by the fact that the alternation of both peripheral [222,223] and brain oxylipin [223–226] by dietary intervention has been demonstrated in animal models. These studies also indicated that the interplay of oxylipin regulation and isoform-specific APOE functions may affect risks factors of neurodegeneration presented in both CNS and peripheral. Therefore, such an interplay of oxylipins and APOE has important implication in neurodegenerative disorders. Whether the oxylipin-APOE relationship is mediated by the esterified oxylipins in ApoE-lipoproteins is yet to be investigated; however, it is clear that reduced HDL ApoE levels are associated with HDL oxylipin enrichment in periphery, suggesting a plausible link between ApoE functionality and lipoprotein oxylipin content [99,227].

5.2.2. The composition-function relationship of HDL can be one of the keys to understand the separate yet interconnected apolipoprotein/lipoprotein system in peripheral and CNS

The CNS and the periphery have a separate yet interconnected lipoprotein formation and transport systems [228], and both are important to many disorders including neurodegenerative diseases (reviewed in [229,230]). In both periphery and CNS, HDL can be formed through the cholesterol efflux and incorporation of cellular lipids by the functions of ABCA1 [231] and ABCG1 [232,233], followed by further maturation by LCAT transesterification [234]. Some of the major differences between the 2 systems include: ApoA1 is the major apolipoprotein in peripheral HDL [235], and ApoE is much less abundant components compared to ApoA1 in periphery overall [236] even though about half of peripheral ApoE is distributed in HDL [237,238] in a isoform-specific manner [237]. Differently, both ApoE and ApoA1 are major apolipoproteins in CSF participating in forming lipoproteins with the size ranging from HDL to LDL [239–241]. Brain ApoA protein are mainly produced outside of the brain, but they enter the CNS from blood [228,242,243]; a portion of them can also be produced by the brain capillary endothelial cells [244,245]. Differently, ApoE from peripheral (produced in liver and other sites [243,246]) cannot enter CNS [247,248]. In terms of lipoproteins, only small HDL can cross the blood brain barrier (BBB) [249], which may have important implication in peripheral-CNS connections [228]. Peripheral apolipoprotein/lipoprotein components, such as HDL-cholesterol, ApoE, ApoA and ApoJ can be associated with the level of brain disorders (reviewed in [44]). However, a clearer understanding on the connections between the periphery and the CNS is yet to obtained.

To address this, it is important to investigate how the lipoprotein-related neurodegeneration risks factors, on both sides of BBB, can be altered by the lipoprotein's compositions, particularly oxylipins. Recently, a study pointed to the lipid signatures of AD human brain from APOEε3/3, APOEε3/4 and APOEε4/4 carriers, where the presence of APOE4 isoforms was associated with higher phosphatidylglycerol but lower in other phospholipid species, such as phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, sphingomyelin, lysophosphatidylethanolamine, and phosphatidic acid [208]. The phospholipid profile in APOE3 and APOE4 mice astrocytes-derived lipoproteins had a similar trend except for phosphatidylglycerol. In the same study, APOE4 lipoprotein with changed lipid composition have worse microglia regulation on Aβ and the capacity to improve Aβ-induced cognitive impairment compared to APOE3 lipoprotein in a rodent model [208]. Though it is not known whether this APOE and phospholipid-related functional change of lipoprotein is also mediated by their oxylipins, the incorporation and the release of oxylipins from phospholipid are varied by the phospholipid classes as well as the oxylipin species [124,125] and APOE genotype indeed change overall oxylipin compositions in brain and periphery [199,221]. Therefore, the specific distribution of oxylipins in lipoproteins may play a role in their AD-related and APOE-related functional changes, and thus the investigation on the composition-function relationship for lipoprotein oxylipins are warranted in the context of neurodegenerative disorders. Currently, such investigation is highly limited in the field of neurodegeneration. Even so, the functional changes of HDL due to their compositional changes, especially their oxylipin compositions, are demonstrated in other contexts, as described in the previous sessions [78,163–165]. The composition-function relationships of HDL in periphery may be translatable in the context of neurodegeneration, especially considering that the small HDL can cross over peripheral and CNS [228,249]. Though ApoE-lipoprotein cannot cross BBB [247,248], its production in CNS and

potential change of functions due to the incorporation of oxylipins have important implications on APOE isoform-specific lipid metabolism in CNS [208,211,212] and other AD-related pathological mechanisms [207–210], considering ApoE-lipoprotein can be formed both in CNS and periphery [228,250,251].

5.2.3. The unexplored yet exciting area: The unknown lipoprotein oxylipins in CNS and their potential implications in neurodegeneration

Though oxylipin transport via brain lipoproteins has not been characterized, one may find inspiration on the similarity between microglia and macrophages due to their highly equivalent functions in the brain and in peripheral, respectively, in both immune response and lipid transport. Though peripheral macrophages and microglia (i.e. resident macrophages of central nervous system) have different origins, the former can also infiltrate the brain; they both have important functions in phagocytosis and secretion of inflammatory regulating compounds [252–256], and they shared many biomarkers [257,258]. What's more, both microglia and macrophages participate in the cholesterol efflux through ABCA1 and ABCG1 [231–233,259] and the production of apolipoproteins [260–262] for lipoprotein formation. In pathological scenarios, the abnormal lipid accumulation in macrophage after absorption of LDL or oxLDL results in foam cells, whose aggregation is critical in forming the proinflammatory atherosclerotic plaque and damaged artery (reviewed in [40]). Similarly, the abnormal lipid accumulation in microglial can be caused by inflammatory stress [263] and the lipid droplet accumulating microglia is highly pro-inflammatory [264]. Both macrophage and microglia are essential for vascular functions [40,265]. As mentioned above, evidence showed that oxylipins can be effluxed from macrophages to ApoA1 through the ABCA1 complex. The transportation of cellular oxylipins from microglia to ApoE or ApoE-lipoprotein is expected to be similar to the one from macrophage to ApoA or ApoA-lipoprotein, but it requires further investigation to test such hypothesis. Such investigation can be important to explain why the alternation of microglial APOE gene expression and protein expression are critical for neural assaults (e.g. inflammatory stimuli of LPS [266], traumatic brain injury [267] or neurodegenerative diseases [268]), even though microglia is not the main producer of ApoE in the CNS system [183,266]. Such investigation may also provide critical insight into why such responses can be APOE isoform-specific [266].

5.2.4. The potential roles of lipoprotein oxylipins in the peripheral-central connection in infectious diseases: a possible component to bridge peripheral and CNS symptoms

Infectious diseases like COVID-19 can cause both peripheral and CNS symptoms [269,270]; its pathologies also involves dysregulation in both oxylipins [24,25] and lipoproteins [41,42], which makes it an interesting disease model to investigate the roles of lipoprotein oxylipins across periphery and CNS. Considering the potential roles of lipoprotein oxylipins in immune regulation [76] [78], their involvement in the peripheral and central symptoms in COVID-19 is highly likely.

Prolonged neurologically related symptoms as a part of "post-acute sequelae of SARS-CoV-2 infection (PASC)" (i.e., "long COVID" or "long-haul COVID") include fatigue sensation, headache, dysregulation in olfactory, gustatory and sleep functions, anxiety, depression and cognitive impairment [271–274]. The chronic PASC neurological symptoms have been associated with abnormal resolution in systemic inflammation [275,276], dysregulation in vascular functions [277,278] and the viral infection targeting the lipoprotein-producing choroid plexus epithelial cells across blood-CSF barriers [279]. Consistent with these characteristics linking COVID-19 peripheral and central symptoms, the correlation of altered circulating oxylipin profile and COVID-19 severity points to the dysregulation of inflammation resolution [25,26]. Mechanistically, the oxylipin composition of circulating lipoproteins can modify the interaction between lipoproteins and endothelial cells, which is therefore implicated in their impact on vascular functions [34]. Furthermore, the incorporation of esterified and free oxylipins in lipoproteins can change the characteristics of lipoproteins [34,76,78,163–165], and virus infections are often closely associated with the cellular production of lipoproteins of the hosts, not only in periphery [280,281] but also across periphery and CNS [279]. In addition, relatable to neurodegenerative diseases, APOE genotype is also a risk factor for the COVID susceptibility and severity [278,282,283], which may be related to how APOE affect lipoprotein lipid compositions [99,208], the oxylipin composition in particular [199,221], and their resulting change of functionality [34,76,78,163–165,227] while interacting with viral receptor ACE2 [283]. Therefore, the involvement of lipoprotein oxylipins in infectious diseases like COVID is warranted, but it requires careful experimental confirmation. This investigation may introduce opportunities such as accurately predicting the severity of infectious diseases based on lipoprotein oxylipins or developing novel treatments targeting lipoprotein oxylipins for these diseases.

6. Conclusion

Oxylipins in free or esterified forms can originate from various pathways. The important autocrine function of oxylipins has been established, but it is not enough to explain their intriguing involvement in the systematic disorders related to inflammation in peripheral and CNS. Evidence has shown that lipoprotein can incorporate cellular oxylipins in esterified forms, which may enable oxylipins to become endocrine regulators for inflammatory responses mediated by lipoprotein transport and lipase-mediated mechanisms. This may explain the heavy involvement of lipoproteins and oxylipins in disorders both in periphery and in brains, which has important implications in both cardiometabolic and neurological disorders.

As for future directions, a lipoprotein isolation method that can achieve higher resolution, shorter experiment time, and good compatibility to other detection tools such MS/MS will be highly desired. In addition, the synthesis of isotopically labeled oxylipins esterified in complex lipids will highly benefit the analysis of esterified oxylipin not only in lipoproteins but also in other biological samples. Furthermore, the esterified oxylipins in lipoproteins and other compartments should be profiled in bigger, well-characterized cohorts to connect this area of biology with other parts of metabolism, genetic makeup, and cardiometabolic and neurological disease outcomes. Such studies are critical to link the inflammatory dysregulation in the peripheral to the one in CNS, as well as to link the potential biomarkers and actionable intervention related to oxylipins and lipoproteins to the precision medical care to target the so-far untreatable neurodegenerative diseases. This approach will provide data-driven target selection for more detailed studies in models in vitro and in vivo.

Declaration of Competing Interest

Kamil Borkowski (through Duke University/UC Davis) is a co-inventor for a patent targeting Alzheimer's disease lipid mediators. Rima Kaddurah-Daouk is an inventor for several patents on the application of metabolomics for the diagnosis and treatment of CNS diseases and holds equity in Metabolon Inc., Chymia LLC and PsyProtix, which were not involved in this study. All other authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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