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Oxidized phospholipids are biomarkers, drug targets, and drug leads

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Enzymatic oxidation or autooxidation of esterified polyunsaturated fatty acids (PUFA) residues within phospholipids in cell membranes or circulating lipoprotein particles leads to the formation of a broad range of oxidized phospholipid (OxPL) species. Chronically elevated OxPL levels present in circulation and atherosclerotic plaques are thought to induce proinflammatory and injurious effects on blood- and vessel wall cells. However, analysis of the structure-activity relationship also identified specific OxPL products exhibiting prominent anti-inflammatory, pro-survival and barrier protective properties. This minireview will briefly summarize rapidly accumulating evidence pointing to the importance of OxPLs in pathology, where they can play multiple roles of biomarkers, drug targets and drug leads.

KEYWORDS

endothelium, permeability, lung injury, inflammation, toll-like receptor inhibition, endothelial cell barrier protection, alkyl-amide oxidized phospholipids

Introduction

Membrane PLs contain the major cellular pool of PUFAs, which can be oxidized enzymatically or non-enzymatically thus producing biologically active oxidized phospholipids (OxPLs, Figure 1) (Hajeyah et al., 2020; Spickett, 2020). During the last two decades OxPLs have been extensively characterized as drivers of pathology in multiple

Abbreviations: AOAH, acyloxyacyl hydrolase; apo(a), apolipoprotein a; apoB-100, apolipoprotein B-100; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; KOdiA-PC, 1-palmitoyl-2-(5-keto-6-octene-dioyl)-sn-glycero-3-phosphocholine; KDdiA-PC, 1-palmitoyl-2-(4-keto-dodec-3-enadioyl)-sn-glycero-3-phosphocholine; LBP, lipopolysaccharide binding protein; LDL, low density lipoproteins; Lp(a), lipoprotein (a); LPS, bacterial wall lipopolysaccharide; OxLDL, oxidized low-density lipoprotein; OxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; OxPE, oxidized phosphatidylethanolamine; OxPL, oxidized phospholipid; OxPS, oxidized phosphatidylserine; PAF, platelet-activating factor; PAF-AH, PAF acetylhydrolase; PL, phospholipid; PEIPC, 1-palmitoyl-2-(5′,6′-epoxyisoprostane E2)-*sn*-glycero-3-phosphocholine; PGPC, 1-palmitoyl-2-(9′-glutaroyl)-*sn*-glycero-3-phosphocholine; PONPC, 1-palmitoyl-2-(9′-oxononanoyl)-*sn*-glycero-3-phosphocholine; POVPC, 1-palmitoyl-2-(5′-oxovaleroyl)-*sn*-glycero-3-phosphocholine; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; RNS, reactive nitrogen species; TLR, Toll-like receptor.

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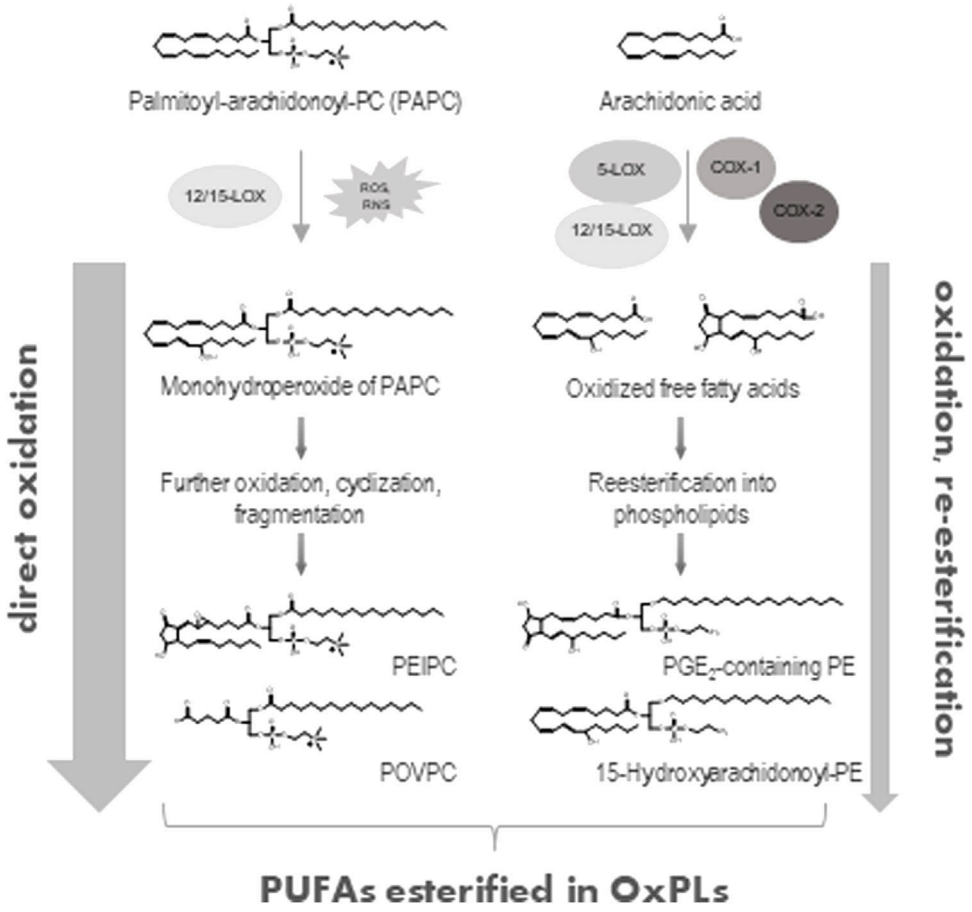

FIGURE 1
Generation of OxPLs. Direct oxidation of PUFA-containing phospholipids either *via* enzymatic (12/15-lipoxygenase, 12/15-LOX) or non-enzymatic (ROS- or RNS-mediated) reactions represents the major way of formation of OxPLs (left part). Alternatively, free, unesterified PUFAs (e.g., arachidonic acid) can be directly oxidized by lipoxygenases (5- or 12/15-LOX) or cycloxygenases (COX-1 or COX-2) and then esterified to a lyso-PL with generation of OxPLs (right part). Only few examples of possible OxPL structures are shown.

inflammatory and metabolic conditions. This minireview will focus on the emerging role of OxPLs in medicine and pharmacology, where they are increasingly recognized as disease markers, drug targets and drug leads.

Oxidized phospholipids as biomarkers of chronic vascular disease and acute inflammation

Oxidative stress is a major mechanism underlying atherogenesis and cardiovascular disease. OxPLs represent a group of oxidation-generated lipids, some of which can covalently bind to proteins and form so-called oxidation-specific epitopes recognized by the innate and adaptive immunity. Such molecules accumulate in OxLDL and atherosclerotic plaques (Gugiu et al., 2008; Gonen et al., 2019) and stimulate chronic inflammation and deposition of lipids (Podrez et al., 2007; Bartolini Gritti and Binder, 2016). OxPLs are especially abundant in circulating apoB-100-containing lipoproteins LDL and Lp(a), where they are present both as free lipids and covalent complexes with apoB or apo(a) (Leibundgut et al., 2013). An established immune assay for circulating OxPLs is based on a monoclonal antibody E06, which recognizes oxidized phosphatidylcholine. Levels of OxPLs are normalized to the apoB-100 and therefore the readout is referred to as an OxPL-apoB ratio (Tsimikas et al., 2005). Multiple clinical association studies using the OxPL-apoB assay have shown correlation of OxPL-apoB levels with the progression, acute cardiovascular events, and efficiency of therapy of cardiovascular disease (Taleb et al., 2011; Byun et al., 2015; Capoulade et al., 2015; Byun et al., 2017). In addition, generation of OxPL products has been reported in various non-infectious (Philippova et al., 2019; Ademowo et al.,

TABLE 1 Role of elevated OxPL products in various inflammatory diseases in humans and rodent models.

Type of inflammatory condition	Model	OxPL compound	Value	References
Atherosclerosis and CAD	Human plasma and atheroscle-rotic plaques	OxPC	OxPC are associated with progression of the cardiovascular disease and its complications	Gugiu et al. (2008), Taleb et al. (2011), Byun et al. (2015), Capoulade et al. (2015), Byun et al. (2017), Gonen et al. (2019)
	Mice	OxPC, POVPC	Antibodies scavenging OxPC lead to inhibition of development of atherosclerotic events: - Lesser cholesterol accumulation in mice vessels - Less aorta calcification - Lower phagocytic activity of macrophages	Tsimikas et al. (2011), Que et al. (2018), Cherepanova et al. (2020), Gao et al. (2020)
	Mice	OxPC, POVPC	Antibodies scavenging OxPC lead to impaired inflammatory status - Inhibition of OxPL-induced IL-1ß and TNFα - Increased expression of inflammation suppressors	Que et al. (2018), Yeang et al. (2019), Cherepanova et al. (2020)
Ischemia-reperfusion injury	Rat cardio-myocytes; *ex vivo* model using rat hearts; rats	Different molecular species: OxPC, OxPE, OxPS	Antibodies scavenging OxPC - Ameliorate cell death in cardiomyocytes under ischemia-reperfusion stress conditions - Reduce myocardial ischemia-reperfusion injury	Yeang et al. (2019), Bagchi et al. (2020), Solati et al. (2021), Stamenkovic et al. (2021), Ma et al. (2022)
Coagulation	Mouse models of hyperlipidemia; human plasma	Short-chain and long-chain OxPLs	Platelet hyperactivity and accelerated thrombosis caused by OxPLs	Podrez et al. (2002), Podrez et al. (2007), Zimman and Podrez (2010), Biswas et al. (2017)
Inflammatory pain	Mice	OxPC	Antibodies scavenging OxPC lead to lower nociception caused by OxPLs	Mohammadi et al. (2018)
Steatohepatitis and fibrosis models	Mice	OxPC	Antibodies scavenging OxPC reduce hepatic cholesterol and triglycerides	Imai et al. (2008)
	Mice	OxPC, various molecular species identified by LC-MS/MS	Scavenging OxPLs by expressed specific antibodies prevents the progression of steatohepatitis to fibrosis	Upchurch et al. (2022)
Osteoporosis	Mice; rats	OxPC	Antibodies scavenging OxPC attenuate bone loss	Ambrogini et al. (2018), Palmieri et al. (2021)
Acute lung injury	Human plasma	OxPC	SARS-CoV-2 infection is accompanied by elevated OxPLs in plasma	Akpinar et al. (2021)
	Mice	OxPC	Accumulation of OxPC is linked to a pro-inflammatory state induced by H5N1 avian flu, SARS, or intratracheal instillation of hydrochloric acid	Imai et al. (2008)
	Mice	Short-chain OxPC	Exacerbating acute lung injury in the aging lungs	Ke et al. (2019)
	Mice	Hydroperoxides of PC	Vascular damage during lung ischemia reperfusion injury *via* formation of OxPLs	Li et al. (2022)
	Mice	Epoxidized PLs as a source of epoxy fatty acids	Epoxy-fatty acids released from PLs or applied exogenously induce vascular remodeling and alleviation of pulmonary hypertension	Moriyama et al. (2022)
Parkinson, Alzheimer, Huntington diseases	Neuronal cells; human plasma; cell-free experiments; cells, *ex vivo* brain slices from rats; mouse models	PONPC, hydroperoxide of PC, POVPC, oxidized cardiolipins	- Level of POVPC is higher in plasma of Alzheimer patients. - POVPC induces loss of GSH and a mitochondrial bioenergetic deficit in neuronal cells. - Accelerated amyloidogenesis induced by PONPC or lipid bilayers contained hydroperoxide PCs. Prevention of lipid peroxidation: - Lowers calcium influx - Diminishes neuronal death induced by α-synuclein aggregates	Mahalka et al. (2011), Artyukhova et al. (2019), Ademowo et al. (2020a), Ademowo et al. (2020b), Angelova et al. (2020), Espinosa et al. (2022)

(Continued on following page)

TABLE 1 (*Continued*) Role of elevated OxPL products in various inflammatory diseases in humans and rodent models.

Type of inflammatory condition	Model	OxPL compound	Value	References
Rheumatoid arthritis	Mice	OxPC	Antibodies scavenging OxPC or antioxidants preventing PL oxidation/ferroptosis hampers progression of rheumatoid arthritis	Oehler et al. (2017), Jhun et al. (2020)
Multiple sclerosis	Mice; human brains	OxPC	Microglia mediate clearance of OxPC as the driver of neurodegeneration	Qin et al. (2007), Dong et al. (2021)
Type-2 diabetes	Human serum	Monohydroxides of OxPC	Long chain OxPCs are slightly elevated in patients with insulin resistance as compared to the control individuals	Godzien et al. (2019)
	Zebra fish model	Hydroperoxides of PC and PE	Accumulation of OxPLs is observed in this model	Chen et al. (2018)
Traumatic brain injury	Human, mouse or rat brains	Peroxidized PEs, PSs and cardiolipins	- Oxidized PEs drive ferroptosis in cells upon brain trauma - Oxidized PSs mediate efferocytosis and injury resolution - Oxidized cardiolipins induce apoptosis after brain trauma	Bayir et al. (2007), Kagan et al. (2017), Wenzel et al. (2017)
Renal failure	Mice; human urine cell pellets	PC- and cardiolipin hydroperoxides	Excessive lipid peroxidation leads to renal failure	Skouta et al. (2014), Friedmann Angeli et al. (2014), Wenzel et al. (2017)
Allergy, asthma, pulmonary hypertension	Mouse and human mast cells; mice	PLs containing epoxy fatty acids	Peroxidized phospholipids with epoxy-fatty acids are responsible for development of allergy and asthma signs	Shimanaka et al. (2017), Moriyama et al. (2022)
Aging	Rats; mice	Short-chain OxPLs, long-chain OxPLs	- Age-related increase in OxPLs was paralleled to rat memory impairment - Aged rats have less peroxiredoxin 6, which has a dual PL hydroperoxide reductive and phospholipase A_2 cleaving activities, and have impaired spatial memory and abnormal synaptic plasticity - Peroxiredoxin 6 deficient mice exhibited anxiety-like behavior, enhanced contextual fear memory, and impaired spatial memory - Elevated in plasma levels of short-chain OxPLs augment pre-existing pro-inflammatory events	Liu et al. (2013), Ke et al. (2019), Lubec et al. (2019), Narzt et al. (2022), Pairojana et al. (2022)
UV-light exposure	Human skin explants; mouse skin; keratinocytes	PE hydroperoxides, oxidized cardiolipins	UVB-light induces skin damage	Vats et al. (2021)
	Human skin; keratinocytes; mice	Short-chain OxPLs	UVB-light induces systemic immunosuppression through formation of short-chain OxPLs	Sahu et al. (2012)
Cancer	Cancer cell lines	POVPC	Metastatic potential of cancer cells is increased	Seok et al. (2021)
Radio-and chemotherapy	Human subjects; cells; mice	Short-chain OxPLs	- Radiation and chemotherapy generate short-chain OxPLs - OxPLs formed promote treatment failure (augment tumor growth and modulate immune responses in hosts)	Sahu et al. (2015), Sahu et al. (2016)
Acute alcohol exposure	Keratinocytes; human and murine skin *ex vivo* models; rats	Short-chain OxPLs	Alcohol consumption leads to generation of OxPLs and: - Amplify the systemic immunosuppression - Induce skin damage when combined with UV-light exposure - Induces kidney injury	Yang et al. (2010), Latchoumycandane et al. (2014), Harrison et al. (2018), Appolonia et al. (2022)

2020a; Solati et al., 2021) and infectious (Imai et al., 2008; Matt et al., 2015) diseases including COVID-19 (Akpinar et al., 2021). Importantly, several disease associations mentioned above have been independently confirmed by mass spectrometry-based methods, although such studies are relatively scarce in comparison to immune methods. An advantage of mass spectrometry is the ability to quantify different classes of OxPLs. Available publications on the clinical measurements of different classes and molecular species of OxPLs by ELISA or mass spectrometry are summarized in the Table 1.

Open question: How direct is the relation between circulating levels of OxPLs and their pathological impact?

It is incorrect to limit the analysis of OxPLs solely with quantification of their circulating concentrations because the pathological impact depends on the balance of plasma concentrations and activity of protective mechanisms. We have developed an antibody-based *in vitro* test showing that human plasma contains components that either degrade or physically mask OxPLs thus potentially preventing interaction of OxPLs with cellular targets (Bochkov et al., 2016). This "masking" assay demonstrated a significant negative correlation between the masking capacity and atherosclerosis risk factors such as age, smoking, hypertension and family history of CAD (Bochkov et al., 2016). Furthermore, masking capacity negatively correlated with the presence of cardiovascular disease and acute events. In other words, cardiovascular risk burden in patients is accompanied with a weaker masking activity for circulating OxPLs, which can promote disease progression. Further work is needed to establish if a combination of the OxPL-apoB and masking assays can increase their diagnostic power.

Oxidized phospholipids as potential drug targets

The interest to OxPLs is not limited by their role as oxidative stress biomarkers. A large body of data suggests that OxPLs are likely to be active drivers of disease. By analogy with the effects of protein modifications on protein functions, one can say that oxidation induces a gain of function changes in PLs because OxPLs can trigger biological effects that cannot be induced by their non-oxidized precursors. Multiple (patho)physiological activities of OxPLs have been described including those related to innate and acquired immunity, blood clotting, atheroma formation, pain control, etc. (Bochkov et al., 2010; Karki and Birukov, 2021; Zhivaki and Kagan, 2022).

Animal models confirmed the importance of OxPLs in conditions of acute and chronic inflammation such as atherosclerosis (Que et al., 2018), nonalcoholic fatty liver disease (Sun et al., 2020; Upchurch et al. 2022), ischemia-reperfusion injury (Yeang et al., 2019) and osteoporosis (Ambrogini et al., 2018). In combination with human disease association data descried above, these results strongly support the causative involvement of OxPLs in the disease pathogenesis. Therefore, it is tempting to speculate that therapy directed at the neutralization of toxic and pro-inflammatory effects of OxPLs may help to cure human disease.

There are several experimental approaches targeting OxPLs *in vivo*. In addition to passive immunization with antibodies to OxPLs (Oehler et al., 2017), titers of natural anti-OxPL antibodies can be elevated by the immunization with *Streptococcus pneumonia* (Binder et al., 2003). Another approach is the use of anti-inflammatory and anti-atherogenic apoAI-mimetic peptides, which have high affinity to OxPLs and can inhibit their negative effects (Van Lenten et al., 2008; Getz and Reardon, 2011; Oehler et al., 2017). Furthermore, a major part of OxPCs in circulation is bound to Lp(a) and is responsible for pro-inflammatory properties of this lipoprotein (Bergmark et al., 2008; Scipione et al., 2015). Recent clinical trials show that circulating levels of Lp(a) and associated OxPLs can be effectively reduced by RNA-based approaches (Tsimikas et al., 2021). Another promising strategy is a reduction of the pro-inflammatory activities of truncated OxPLs by removing their oxidized acyl chains by administration of a highly conserved host lipase, acyloxyacyl hydrolase (AOAH) (Zou et al., 2021) or platelet-activating factor (PAF) acetylhydrolases (PAF-AHs) (McIntyre, 2012). Last but not least, it is known that pro-inflammatory signaling pathways induced by OxPLs at least partially differ from the pathways activated by classical inflammatory mediators such as TNFα, IL-1β, etc. (Bochkov et al., 2002a; Gargalovic et al., 2006). Thus, selective targeting of OxPLs-induced signal transduction potentially can prevent negative effects of OxPLs without impairing the normal inflammatory signaling.

Oxidized phospholipids as potential drug leads

Well-investigated families of lipid mediators, e.g., prostanoids, induce variable and often functionally opposite effects mediated by different receptors expressed in different cell types. In full agreement with this mode of action, under different biological conditions OxPLs can be either toxic and pro-inflammatory, or they can exhibit protective effects (Figure 2). It has been shown that OxPLs inhibit activation of Toll-like receptor 4 (TLR4) (Bochkov et al., 2002b), well recognized for its role in triggering sepsis. The effect of OxPLs *in vivo* was strong enough to protect animals from lethal doses of LPS (Bochkov et al., 2002b). An important anti-LPS mechanism is the mutually exclusive binding (antagonism) of OxPLs with TLR4 and its

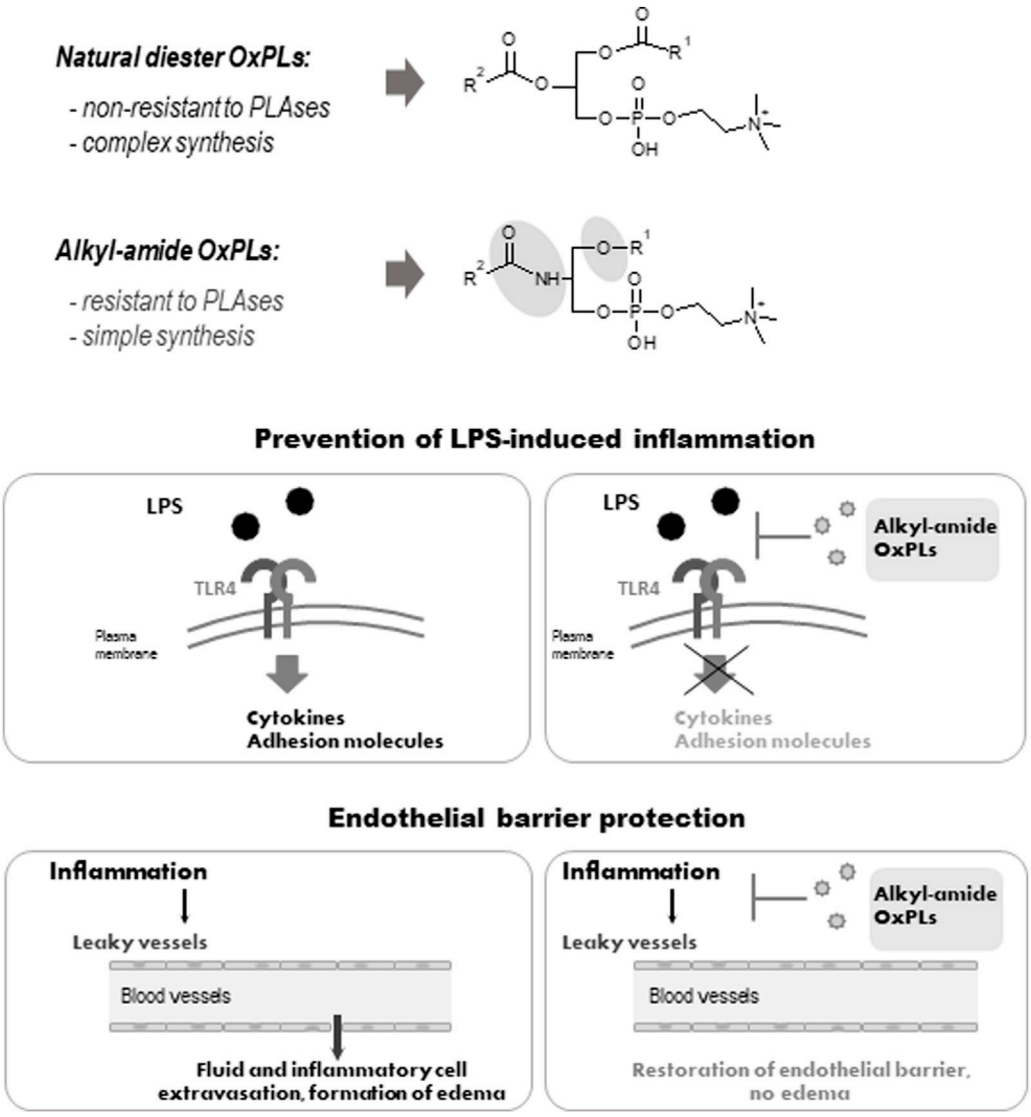

FIGURE 2
Structure and biological activity of alkyl-amide OxPLs. Fatty acid residues are linked *via* an *sn*-1 ether or an *sn*-2 amide bond of alkyl-amide OxPLs respectively, which simplifies their synthesis (upper panel). Alkyl-amide OxPLs inhibit LPS-induced inflammation (middle panel) and enhance lung endothelial barrier (lower panel) *in vitro* and *in vivo* (Oskolkova et al., 2021).

accessory proteins MD-2, CD14 and LBP (Bochkov et al., 2002b; Erridge et al., 2006).

Another potentially beneficial property of OxPLs is their ability to enhance the lung endothelial barrier under basal conditions and after treatment with pathological stimuli such as bacteria, edemagenic bioactive peptides, inflammatory cytokines (TNFα, IL-6) and pathologic mechanical forces (Nonas et al., 2008; Karki and Birukov, 2020). These barrier-protective properties may be beneficial in treatment of sepsis-associated inflammation and its frequent complication—pulmonary edema. As compared to other molecules enhancing lung barrier, such as prostaglandins E_2, and I_2, the barrier-enhancing action of OxPAPC continues for significantly longer time. The efficiency of OxPLs in the prevention of sepsis and lung edema in animal models, as well as underlying molecular mechanisms, have been reviewed recently (Karki and Birukov, 2021).

The data presented above show that non-truncated OxPLs exhibit a unique combination of beneficial properties. They inhibit inflammation induced by bacteria, and at the same time act as long-acting enhancers of endothelial lung barrier. Such a combination may be especially beneficial for treatment of ARDS, where both bacterial inflammation and lung edema play an important role (Karki and Birukov, 2021). However, *in vivo*

application of OxPLs is complicated by rapid degradation of diacyl OxPLs by phospholipases A_1/A_2. To improve pharmacokinetics, we have synthesized OxPLs in which fatty acid residues are bound with glycerol *via* an alkyl and an amide bonds. These bonds are not non-physiological: a large proportion of cellular phospholipids contains *sn*-1 alkyl bond, while an amide bond is typical for sphingolipids, which are also abundant in cells. We found that alkyl-amide OxPLs had good solubility, improved *in vivo* stability and demonstrated anti-LPS and barrier protective effects that were similar to the action of diacyl OxPAPC *in vitro* and in animal models (Figure 2). Thus, alkyl-amide OxPLs represent an improved hit for further development of a drug with polypharmacological activity simultaneously protecting against bacterial sepsis and pulmonary edema.

Given the deleterious effects of chronically elevated OxPLs in cardiovascular pathologies, could modified OxPLs still be beneficial for treatment of patients with pre-existing condition (hyperlipidemia, atherosclerosis, diabetes) suffering from ARDS and other inflammatory syndromes? Both sepsis and lung edema are acute conditions and require short-term application of OxPLs. Therefore, it is unlikely that treatment of such patients with OxPLs-based drugs for hours or days could aggravate concomitant chronic pathologies such as atherosclerosis, which develop during decades.

Conclusion

Similar to other families of lipid mediators, OxPLs may serve as biomarkers of oxidative stress and cardiovascular pathology. Furthermore, OxPLs induce chronic pathological effects, which may be a target for pharmacological neutralization. On the other hand, OxPLs are pharmacological lead structures demonstrating a unique combination of TLR-inhibitory and lung barrier-protective properties. This combination ideally fits for a short-term therapy of systemic inflammation and lung edema. In summary, available data characterize OxPLs as promising structures for further biological analysis and justify their further pharmacological development.

Author contributions

OVO prepared the figures and wrote parts of the manuscript AAB prepared the figures, discussed modifications, edited parts of manuscript. KGB conceived the idea, edited the manuscript and discussed modifications. VNB conceived the idea, wrote the manuscript and discussed modifications.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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