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Review

Characterization of the Structural Diversity and Structure-Specific Behavior of Oxidized Phospholipids by LC-MS/MS

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Polyunsaturated fatty acids (PUFAs), esterified to phospholipids, are susceptible to oxidation. They form oxidized phospholipids (OxPLs) by oxygenases or reactive oxygen species (ROS), or both. These OxPLs are associated with various diseases, such as atherosclerosis, pulmonary injuries, neurodegenerative diseases, cancer, and diabetes. Since many types of OxPLs seem to be generated *in vivo*, precise determination of their structural diversity is required to understand their potential structure-specific functions. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is a powerful method to quantitatively measure the structural diversity of OxPLs present in biological samples. This review outlines recent advances in analytical methods for OxPLs and their physiological relevance in health and diseases.

Key words polyunsaturated fatty acid; oxylipin; oxidized phospholipid; liquid chromatography-tandem mass spectrometry (LC-MS/MS); lipidomics; analytical chemistry

1. Introduction

Phospholipids (PLs) are the major components of cell membranes. Their structures consist of a glycerol backbone with a polar head-group linked to the *sn*-3 position and two fatty acyls linked to the *sn*-1/*sn*-2 positions. Saturated or monounsaturated fatty acids are usually present in the *sn*-1 position. In contrast, polyunsaturated fatty acids (PUFAs), such as linoleic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are mainly located at the *sn*-2 position. PUFA-containing PLs are susceptible to oxidation to form oxidized phospholipids (OxPLs) by reactive oxygen species (ROS) or oxygenases or both. OxPLs display potent biological functions, and their formation and action in many physiological and pathophysiological conditions are of particular interest.^{1–9)}

OxPLs are generated through non-enzymatic and enzymatic reactions. In the non-enzymatic reaction, hydroperoxides are first generated by bis-aryl hydrogen abstraction. They are subsequently converted into oxidized fatty-acyl chains, including truncated fatty acids, α,β -unsaturated fatty acids, and cyclized fatty acids through radical rearrangement¹⁰⁾ (Fig. 1A). While non-enzymatic oxidation randomly generates OxPLs, enzymatic oxidation is likely to form OxPLs structure-specifically. Lipid oxygenases, such as lipoxygenase (LOX), cyclooxygenase (COX), and CYP, catalyze the formation of oxylipins from PUFAs. Among them, Alox12 and Alox15 can directly oxidize PUFA-containing PLs to form OxPLs, such as 12-hydroperoxyeicosatetraenoic acid (12-HpETE)-PL and 15-HpETE-PL, which convert rapidly into the corresponding fatty alco-

hols, namely, 12-hydroxyeicosatetraenoic acid (12-HETE)-PL and 15-HETE-PL by glutathione peroxidase 4 (GPx4)¹¹⁾ (Fig. 1B). OxPLs are also generated by incorporating free oxylipins into cellular PLs by lysophospholipid acyltransferases¹¹⁾ (Fig. 1C). These reactions can generate extensively diverse molecular species of OxPLs *in vivo*. Fedorova and colleagues predicted that by *in silico* calculation, more than 20000 molecular species of OxPLs might exist *in vivo*.¹²⁾

HPLC-UV, the analysis of thiobarbituric acid-reactive substances or immunoassay, or both, have conventionally been used to measure OxPL levels. Still, these methods could not determine the OxPLs' precise fatty-acyl structures.^{9,13–15)} Mass spectrometry (MS)-based lipidomics monitor OxPL levels because of its high sensitivity and selectivity. MS becomes a more potent tool when combined with chromatography separation, such as LC, supercritical fluid chromatography, and ion chromatography.^{16,17)} Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is mainly used to quantitatively monitor OxPL levels in biological samples because this method can separate OxPL molecular species by acyl chain composition and head-group difference.^{18,19)}

2. LC-MS/MS-Based Lipidomics for OxPLs Analysis

LC-MS and LC-MS/MS were utilized for structural identification of OxPLs prepared by auto-oxidation or enzymatic oxidation, or both, including 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine (POVPC), 1-palmitoyl-2-glutaryl-*sn*-glycero-3-phosphocholine (PGPC), 1-palmitoyl-2-(5,6-epoxyisoprostane A2)-*sn*-glycero-3-phosphocholine (PECPC), and

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Fig. 1. OxPL Generation by Non-enzymatic or Enzymatic Reactions

A) Non-enzymatic oxidation of PLs. Hydroperoxy PLs generated by abstracting bis-aryl hydrogen are converted into oxidized fatty-acyl chains, such as truncated fatty acids, cyclized fatty acids, α,β -unsaturated fatty acids, and hydroxy fatty acids through radical rearrangement. B) Enzymatic oxidation of PLs. Hydroperoxy PLs produced by Alox12 or Alox15 direct oxidation are reduced to the corresponding hydroxy PLs by GPx4. C) Free PUFAs are converted into oxylipins by oxygenase, such as COX, LOX, and CYP. Oxylipin-CoAs synthesized by ACSL are incorporated into PLs by LPLATs. (PLA₂; phospholipase A₂, ACSL; long-chain acyl-CoA synthetase, LPLAT; lysophospholipid acyltransferase)

1-palmitoyl-2-(5,6-epoxyisoprostane E2)-*sn*-glycero-3-phosphocholine (PEIPC)^{20,21} (Fig. 2). In atherosclerotic lesions, macrophages take up oxidized LDL particles by scavenger receptors, such as cluster of differentiation 36 (CD36). This process is considered pathogenic due to macrophage foam cells induction.²² Hazen identified OxPLs containing γ -hydroxy(or oxo)- α,β -unsaturated carbonyl moieties, such as 1-palmitoyl-2-(5-hydroxy-8-oxo-6-octenoyl)-*sn*-glycero-3-phosphocholine (HOOA-PC) and 1-palmitoyl-2-(5-hydroxy-8-oxo-6-octenediyl)-*sn*-glycero-3-phosphocholine (HODiA-PC) as a novel family of OxPLs, which serve as potent ligands for CD36^{23–25} (Fig. 2).

Selective reaction monitoring (SRM) using a triple quadrupole mass spectrometer is used for targeted lipidomics of OxPLs by monitoring a specific pair of precursor and fragment ions corresponding to the oxidized fatty-acyl chains at a specified LC retention time.^{26–29} Based on the fragmentation patterns, SRM transitions for each OxPL molecular species monitor target molecules with high selectivity. In addition to

Fig. 2. OxPLs Structures

PGPC; 1-palmitoyl-2-glutaryl-*sn*-glycero-3-phosphocholine, POVPC; 1-palmitoyl-2-(5-oxovaleryl)-*sn*-glycero-3-phosphocholine, PEIPC; 1-palmitoyl-2-(5,6-epoxyisoprostane E2)-*sn*-glycero-3-phosphocholine, PECPC; 1-palmitoyl-2-(5,6-epoxyisoprostane A2)-*sn*-glycero-3-phosphocholine, HOOA-PC; 1-palmitoyl-2-(5-hydroxy-8-oxo-6-octenoyl)-*sn*-glycero-3-phosphocholine, HODiA-PC; 1-palmitoyl-2-(5-hydroxy-8-oxo-6-octenediyl)-*sn*-glycero-3-phosphocholine, PAzPC; 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine, PONPC; 1-palmitoyl-2-(oxo-nonanoyl)-*sn*-glycero-3-phosphocholine, KODiA-PC; 1-palmitoyl-2-(5-keto-6-octene-diyl)-*sn*-glycero-3-phosphocholine.

the optimized SRM channels for synthetic standards, Taguchi and colleagues applied the SRM mode with theoretically expanded datasets. They successfully monitored a series of unknown molecular species of OxPLs.²⁷

Because there can be a substantial overlap in structures between non-enzymatic and enzymatic OxPLs, determining their specific origin in biological samples has been very difficult. O'Donnell and colleagues characterized enzymatically produced OxPLs in various immune cells, such as monocytes, macrophages, platelets, neutrophils, and eosinophils.^{29–33} They first screened OxPLs in murine peritoneal macrophages expressing Alox15 by applying a precursor ion scan of m/z 319.2 (the characteristic ion of $[AA + O^-]$) and identified 12-HETE-PEs by MS/MS analysis.²⁹ They estimated that murine peritoneal lavage from naïve mice contains approximately 5.5-ng 12-HETE-PEs compared with 18.5-ng free 12-HETE by applying the SRM mode.²⁹ These OxPLs are hardly detected in the peritoneal lavage from Alox15^{−/−} mice, suggesting that Alox15 produces those lipids. They applied this procedure to various immune cells and identified endogenous Alox15-, Alox12-, Alox5-, and COX-dependent OxPLs.^{29,31,32,34,35} They confirmed the enzymatic generation of those OxPLs by genetic deletion or pharmacological inhibition for oxygenases. Their excellent protocol for quantitative analysis of enzymatic OxPLs is summarized in ref. 28, including the preparation of OxPL standards, the establishment of calibration curves, and the optimization of analytical conditions.

Untargeted lipidomics, using LC-quadrupole/time-of-flight (QTOF)-MS with information-dependent acquisition mode, monitors OxPLs more widely. This method automatically switches MS to MS/MS by setting the MS/MS trigger at

Fig. 3. MS/MS Spectra of OxPLs

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Fig. 4. OxPL Detection by LC-TripleQ-MS with Optimized SRM Transitions and LC-Gradient Conditions

A) A series of OxPCs containing HETEs was selectively detected by optimized SRM transitions. B) Structural isomers were separated by the optimized LC-gradient conditions. This research was originally published in the *Journal of Lipid Research*. Reproduced from Aoyagi *et al.*³⁸⁾ in slightly modified form.

a low threshold level of intensity. Then, information-rich MS/MS spectra with high resolution are monitored in an unbiased manner.³⁶⁾ O'Donnell and colleagues demonstrated the presence of more than 100 types of OxPLs by applying untargeted lipidomics to the activated human platelets.³⁷⁾ They first putatively characterized all detected ions using online databases, such as LipidMaps, Human Metabolome Database, LipidHome, and METLIN based on m/z values of precursor ions, and then structurally identified the selected ions by MS/MS analysis. However, this procedure did not determine the precise fatty-acyl structures in many OxPLs because the abundance of endogenous OxPLs in human platelets was very low, and the diagnostic fragments of oxidized fatty-acyl chains were hardly detected. To overcome this problem, we developed a comprehensive lipidomics system with high sensitivity by establishing a measured MS/MS spectra library of OxPLs.³⁸⁾ We first biogenically generated OxPLs by adding oxylipins to cultured cells and incorporated into cellular PLs. LC-QTOF-MS-based untargeted lipidomics was used to acquire MS/MS spectral data for the OxPLs (Fig. 3). Based on the MS/MS spectral data for each OxPLs, a broad-targeted lipidomics system was developed by the SRM mode (Fig. 4A). LC-gradient conditions were also optimized for separation of similar structural isomers (Fig. 4B). This novel method could detect OxPLs at levels as low as 10 fmol and monitor a series of enzymatically produced OxPLs in murine peritoneal macrophages. The full MS/MS spectral data are deposited in the "Computational MS-based metabolomics" section of the RIKEN PRIME website (<http://prime.psc.riken.jp/compms/msdial/main.html#MSP>).

3. Formation and Action of OxPLs *in Vivo*

OxPLs have been documented to have pro- and anti-inflammatory effects (Tables 1, 2). Non-enzymatic OxPLs are recognized by scavenger and pattern recognition receptors, such as toll-like receptor 2 (TLR2), TLR4, E-type prostaglandin receptor (EP2), platelet-activating factor receptor (PAFR), noncanonical and nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasomes, and can be considered endogenous damage-associated molecular patterns (DAMPs). Oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (OxPAPC) prepared by auto-oxidation of PAPC is utilized for a representative compound to elucidate the biological action of OxPL. However, the precise biological function of OxPAPC is controversial because OxPAPC is generated as a mixture containing many types of OxPLs, and the quality of OxPAPC is considered largely different by oxidation protocols.³⁹⁾ Since several OxPLs, such as POVPC, PGPC, PEIPC, HOOA-PC, and HODiA-PC, were identified as the dominant molecular species in OxPAPC by LC-MS/MS analysis, the biological activities of individual molecular species have been elucidated.^{20,21,25,40)} Truncated OxPLs, such as POVPC and PGPC inhibit phagocytosis and bacterial clearance *in vivo*.⁴¹⁾ POVPC inhibits lipopolysaccharide (LPS)-induced TLR4 signal by binding to LPS binding protein (LBP) and CD14, which present LPS to TLR4.^{42,43)} Cyclized OxPLs, such as PEIPC and PECPC, induce chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), in endothelial cells. In contrast, they inhibit pro-inflammatory cytokines, such as IL-6 and IL-12 in bone marrow-derived dendritic cells (DCs).^{44–46)} PEIPC can activate EP2 and D-type prostaglandin receptor (DP), inducing adhesion molecules in endothelial cells.⁴⁷⁾ PECPC has a cyclopentenone moiety, which has an α,β -unsaturated carbonyl group, and exerts anti-inflammatory effects by covalent modification of cysteine residues in Kelch-like ECH-associated protein 1 (Keap1), disrupting the NF-E2-related factor 2 (Nrf2)-Keap1 interaction.^{48,49)} When ROS oxidize PCs with an ether bond at the *sn*-1 position, OxPL species similar to the structure of PAF are generated. These PAF-like OxPLs induce Ca^{2+} influx into polymorphonuclear leukocytes (PMNs) by binding to PAFR.^{50–52)} Tanaka and colleagues recently reported that ether OxPLs had been generated in neutrophils during neutrophil extracellular traps (NETs) formation induced by low-dose phorbol 12-myristate 13-acetate (PMA) and sulfasalazine (SSZ), and exogenous application of ether OxPC to neutrophils with PMA induced NETs formation⁵³⁾ (Fig. 5). The roles of OxPLs in inflammasome activities have been controversial.^{54–58)} PGPC and POVPC activate noncanonical and NLRP3 inflammasomes in LPS or Pam3CSK4-primed bone marrow-derived macrophages (BMDMs) and DCs.^{54,55)} Kagan *et al.* showed that those OxPLs could serve as ligands for CD14, and CD14 endocytosis upon OxPL binding promotes noncanonical and NLRP3 inflammasome activation in BMDMs and DCs.⁵⁵⁾ Alternatively, Stehlik and colleagues reported that POVPC and PGPC inhibited LPS-induced noncanonical inflammasome activation in BMDMs but not DCs.⁵⁷⁾ Because OxPLs bind directly to caspase-11 when co-transfected with LPS, it may compete with LPS binding to caspase-11, a cytosolic LPS receptor that promotes noncanonical inflammasome activation.⁵⁴⁾

Enzymatic OxPLs have biological roles in various types of

Table 1. Structures and Functions of Nonenzymatic OxPLs

Name	Structure	Function
POVPC		•Activates TRPA1-induced calcium influx⁸¹⁾ •Induces vascular smooth muscle cell proliferation⁸²⁾ •Induces noncanonical and NLRP3 inflammasome activation in macrophages and DCs⁵⁶⁾ •Inhibits LPS-induced noncanonical inflammasome activation in macrophages⁵⁷⁾ •Induces apoptosis in smooth muscle cells and macrophages^{83–85)} •Induces ceramide accumulation in macrophages⁸⁵⁾ •Inhibits LPS-induced TLR4 signal in endothelial cells⁴²⁾
PGPC		•Activates TRPA1-induced calcium influx⁸¹⁾ •Induces noncanonical and NLRP3 inflammasome activation in macrophages and DCs⁵⁶⁾ •Inhibits LPS-induced noncanonical inflammasome activation in macrophages⁵⁷⁾ •Induces apoptosis in smooth muscle cells and macrophages^{83–85)} •Induces ceramide accumulation in macrophages⁸⁵⁾
PEIPC		•Induces adhesion molecules in endothelial cells by activating EP2 and DP⁴⁷⁾ •Induces chemokines in endothelial cells⁴⁶⁾ •Inhibits pro-inflammatory cytokines in bone marrow derived dendritic cells⁴⁴⁾
PECPC		•Inhibits pro-inflammatory cytokines by covalent modification of cysteine residues in Keap1⁴⁸⁾ •Induces chemokines in endothelial cells⁴⁶⁾ •Inhibits pro-inflammatory cytokines in bone marrow derived dendritic cells⁴⁴⁾
HOOA-PC		•High affinity ligand for CD36²⁵⁾ •Reduces cathepsin B activity in macrophages⁸⁶⁾ •Increases chemokines in endothelial cells⁸⁷⁾
KODiA-PC		•High affinity ligand for CD36²⁵⁾
Ether-linked PC (PAF-like lipid)		•Induces Ca²⁺ influx into PMNs by binding to PAFR⁵²⁾ •Induces NETs formation⁵³⁾ •High affinity ligand for PPARγ⁸⁸⁾ •Induces CD36 expression⁸⁸⁾
PONPC		•Enhances LPS stimulation in mouse alveolar macrophages⁸⁹⁾

immune cells, including platelets, macrophages, eosinophils, DCs, mast cells, and neutrophils^{31,33,59–62)} (Table 2). In murine peritoneal macrophages, Alox15-dependent OxPL production contributes to maintaining immunogenic tolerance by interfering with milk fat globule-EGF factor 8 (MFG-E8)-mediated uptake of apoptotic cells into inflammatory monocytes.⁶¹⁾ Alox15-derived OxPLs may regulate DC maturation and function through Nrf2 activation.⁶²⁾ Ferroptosis, the newly characterized non-apoptotic cell death, was recently reported to be induced by hydroperoxy-PEs generated by the Alox15/PE binding protein 1 (PEBP1) complex.^{63,64)} Bacterial infection activates Alox5 and produces 5-HETE-PE in neutrophils, and exogenous addition of OxPL containing 5-HETE inhibited NETs formation.³¹⁾ OxPLs containing omega-3 PUFA epoxides, such as 17,18-epoxyeicosatetraenoic acid (17,18-EpETE)

and 19,20-epoxydocosapentaenoic acid (19,20-EpDPE) regulate mast cell function through spontaneously providing free omega-3 PUFA epoxides.⁶⁰⁾ Also, OxPLs containing 17,18-EpETE modulate the transient receptor potential (TRP) V4 channel activity by changing the membrane properties.⁶⁵⁾

The relevance of OxPLs with atherosclerosis has been mostly investigated. In clinical studies, immunoassay using E06 antibody, the immunoglobulin M (IgM) natural antibody that recognizes OxPC but not PC, showed that OxPL/apoB-100 levels in plasma were strongly correlated with atherosclerosis progression.^{66–68)} However, this method could not distinguish molecular species of OxPLs and determine the correlation of atherosclerosis progression with individual OxPLs. LC-MS/MS-based quantitative analysis estimated the levels of individual OxPLs, including PGPC, POVPC, 1-palmitoyl-

Table 2. Structures, Formations and Functions of Enzymatic OxPLs

Name	Structure	Formation and function
5-HETE-PC		•Produced by Alox5³¹⁾ •Enhances thrombin generation^{59,90)}
12-HETE-PC		•Produced by Alox12 or Alox15^{35,38)} •Enhances thrombin generation^{59,90)}
15-HETE-PC		•Produced by Alox15²⁸⁾ •Enhances thrombin generation^{59,90)}
5-HETE-PE		•Produced by Alox5³¹⁾ •Enhances thrombin generation^{59,90)} •Inhibits NETs formation³¹⁾
12-HETE-PE		•Produced by Alox12 or Alox15^{35,38)} •Maintains immunologic tolerance in murine peritoneal macrophages⁶¹⁾ •Facilitates autophagy⁹¹⁾ •Enhances thrombin generation^{59,90)} •Inhibits abdominal aortic aneurysm (AAA) development⁹²⁾ •Downregulated in Scott syndrome³⁵⁾
15-HETE-PE		•Produced by Alox15⁹³⁾ •Enhances thrombin generation^{59,90)} •Inhibits LPS-stimulated cytokine production in monocytes²⁹⁾ •Facilitates goblet cell differentiation⁹³⁾
15-HpETE-PE		•Produced by Alox15⁶³⁾ •Upregulated in ferroptotic cells^{63,94,95)} •Activates autophagy⁹⁶⁾ •Promotes cytokine expression through TLR4 activation⁹⁷⁾
14-HDoHE-PE		•Produced by Alox12 or Alox15^{32,38)} •Upregulated in platelets in response to thrombin³²⁾
17,18-EpETE-PL		•Produced by CYP⁹⁸⁾ •Modulates TRPV4 activity⁶⁵⁾
PGE ₂ -PE		•Produced by COX³⁴⁾ •Upregulated in platelets in response to thrombin³⁴⁾
PGD ₂ -PE		•Produced by COX³⁴⁾ •Upregulated in platelets in response to thrombin³⁴⁾
DioxolaneA ₃ -PE		•Produced by COX⁹⁹⁾ •Upregulated in platelets in response to thrombin⁹⁹⁾ •Stimulates neutrophil integrin expression⁹⁹⁾

2-(oxo-nonanoyl)-*sn*-glycero-3-phosphocholine (PONPC), and 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine (PAzPC) to be 1–3 μ M in human atherosclerotic plaques and aortas of aged apoe^{-/-} mice, whereas that in human and mouse plasma was 0.1–1 μ M.^{4,69)} The amounts of OxPLs bound to CD36,

such as HOOA-PC and HODiA-PC, accumulate in the plasma of hyperlipidemic mice up to 40-fold higher than in normolipidemic mice.⁷⁰⁾ Mice lacking Alox15 showed atherosclerosis development attenuation, suggesting that Alox15-derived OxPLs are related to atherosclerosis progression.^{71–74)} In ad-

Fig. 5. Application of LC-MS/MS Analysis to Neutrophils during NETs Formation

A) Ether-linked OxPLs were generated during NETs formation induced by PMA and SSZ. B) Exogenous application of ether-linked OxPC but not ether-linked PC to neutrophils with PMA induced NETs formation. (Color figure can be accessed in the online version.) This research was originally published in *Scientific Reports*. Reused from Yotsumoto *et al.*⁵³⁾ which is licensed under a Creative Commons Attribution 4.0.

dition to atherosclerosis, the molecular species of OxPLs are associated with various diseases. Some truncated OxPLs, such as PGPC, POVPC and PONPC, increased in LPS-induced acute lung injury in mice.⁷⁵⁾ The concentrations of 9-hydroxyoctadecadienoic acid (9-HODE), 13-HODE and 15-HETE in PL were 2-fold higher in HDL from patients with type 2 diabetes than healthy subjects.⁷⁶⁾ PCs containing 9-HODE and 13-HODE were elevated in the sera of patients with breast cancer.⁸⁾ Patients with Alzheimer's disease had higher serum POVPC, and cognitive function was inversely correlated with POVPC.⁵⁾ Recently, Hara *et al.* applied untargeted lipidomics to sera collected from patients with Kawasaki disease and identified OxPLs as elevated lipids in Kawasaki disease's acute phase. Their detailed molecular species were successfully identified as OxPCs containing hydroxy DHAs, such as 7-hydroxydocosahexaenoic acid (7-HDoHE), 10-HDoHE, 14-HDoHE, 17-HDoHE, and 20-HDoHE using a broad-targeted lipidomics system.⁷⁷⁾ While the relevance of OxPLs with diseases has been suggested, the biological roles of OxPLs *in vivo* have been largely unknown due to the difficulty of controlling endogenous OxPL production. Witztum *et al.* recently engineered *Ldlr*^{-/-} mice that express a single-chain variant of the E06 antibody, which neutralizes OxPLs.⁷⁸⁾ Using this transgenic mouse, they showed that the neutralization of OxPL ameliorates the progression of atherosclerosis and nonalcoholic steatohepatitis (NASH), therefore, suggesting that targeting OxPLs is an effective therapeutic strategy for these diseases.^{78,79)}

4. Conclusion

Recent advances in LC-MS/MS enabled us to identify and quantitatively monitor individual molecular species of OxPLs and elucidate their potential structure-specific behavior *in vivo*. However, the molecular mechanisms underlying biological activities and relevance with diseases largely remain to be elucidated. Further researches on the biosynthesis, metabolism, and target proteins at the molecular level would help us to understand the pathophysiological importance of OxPL and lead to discover potential therapeutic candidates for related diseases.

Lipid Nomenclature

Lipid nomenclature used in this review is based on IUPAC-IUBMB recommendation.⁸⁰⁾

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Conflict of Interest The authors declare no conflict of interest.

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