Analytical Chemistry in Biology and Medicine

Review

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

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Received March 30, 2021

Polysaturated 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 polysaturated 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, polysaturated 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. PUFAs-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.  

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, $\alpha,\beta$-unsaturated fatty acids, and cyclized fatty acids through radical rearrangement. While non-enzymatic oxidation randomly generates OxPLs, enzymatic oxidation is likely to form OxPLs structure-specifically. Lipid oxygenases, such as lipoxigenase (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 alcohols, namely, 12-hydroxyoctadecatrienoic acid (12-HETE)-PL and 15-HETE-PL by glutathione peroxidase 4 (GPx4) (Fig. 1B). OxPLs are also generated by incorporating free oxylipins into cellular PLs by lysophospholipid acyltransferases (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.

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. 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. 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.

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-glutaroyl-sn-glycero-3-phosphocholine (PGPC), 1-palmitoyl-2-(5,6-epoxyisoprostane A2)-sn-glycero-3-phosphocholine (PECPC), and...
1-palmitoyl-2-(5,6-epoxyisoprostane E2)-sn-glycero-3-phosphocholine (PEIPC) (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. 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; 1-palmitoyl-2-(5-hydroxy-8-oxo-6-octenedioyl)-sn-glycero-3-phosphocholine, HOdiA-PC; 1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine, PAzPC; 1-palmitoyl-2-(oxo-nanoyl)-sn-glycero-3-phosphocholine, KOiA-PC; 1-palmitoyl-2-(5-keto-6-octene-dioyl)-sn-glycero-3-phosphocholine.

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. Based on the fragmentation patterns, SRM transitions for each OxPL molecular species monitor target molecules with high selectivity. In addition to 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.

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. 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. 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. 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 as a novel family of OxPLs, which serve as potent ligands for CD36.

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

This research was originally published in the *Journal of Lipid Research*. Reused from Aoyagi et al.\(^{38}\) which is licensed under a Creative Commons Attribution 4.0 (http://creativecommons.org/licenses/by/4.0/).
Sensitivity by establishing a measured MS/MS spectra library developed a comprehensive lipidomics system with high sensitivity. However, this procedure did not determine the precise fatty-acyl structures in many OxPLs because the MS/MS analysis. However, this 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. Since several OxPLs, such as POVPC, PGPC, PEIPC, HOOA-PC, and HOdiA-PC, were identified as the dominant molecular species in OxPL by LC-MS/MS analysis, the biological activities of individual molecular species have been elucidated. Truncated OxPLs, such as POVPC and PGPC inhibit phagocytosis and bacterial clearance in vivo. POVPc inhibits lipopolysaccharide (LPS)-induced TLR4 signal by binding to LPS binding protein (LBP) and CD14, which present LPS to TLR4. Cyclized OxPLs, such as PEIPC and PEPC, induce chemokines, such as monocyte chemotactic 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). PEIPC can activate EP2 and D-type prostaglandin receptor (DP), inducing adhesion molecules in endothelial cells. 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. 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 Ca2+ influx into polymorphonuclear leukocytes (PMNs) by binding to PAFR. 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 formation. The roles of OxPLs in inflammasome activities have been controversial. PGPC and POVPc activate noncanonical and NLRP3 inflammasomes in BMDMs and DCs. 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. Alternately, Stehlik and colleagues reported that POVPc and PGPC inhibited LPS-induced noncanonical inflammasome activation in BMDMs but not DCs. 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.

Enzymatic OxPLs have biological roles in various types of...
immune cells, including platelets, macrophages, eosinophils, DCs, mast cells, and neutrophils\textsuperscript{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.\textsuperscript{61) Alox15-derived OxPLs may regulate DC maturation and function through Nrf2 activation.\textsuperscript{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.\textsuperscript{63,64) Bacterial infection activates Alox5 and produces 5-HETE-PE in neutrophils, and exogenous addition of OxPL containing 5-HETE inhibited NETs formation.\textsuperscript{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 macrophage function through spontaneously providing free omega-3 PUFA epoxides.\textsuperscript{60) Also, OxPLs containing 17,18-EpETE modulate the transient receptor potential (TRP) V4 channel activity by changing the membrane properties.\textsuperscript{65) The relevance of OxPLs with atherosclerosis has been most likely 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.\textsuperscript{66–68) However, this method could not distinguish molecular species of OxPLs and determine the correlation of atherosclerosis progression with individual OxPLs.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Name} & \textbf{Structure} & \textbf{Function} \\
\hline
POVPC & & \begin{itemize}
\item Activates TRPA1-induced calcium influx\textsuperscript{81)}
\item Induces vascular smooth muscle cell proliferation\textsuperscript{82)}
\item Induces noncanonical and NLRP3 inflammasome activation in macrophages and DCs\textsuperscript{66)}
\item Inhibits LPS-induced noncanonical inflammasome activation in macrophages\textsuperscript{67)}
\item Induces apoptosis in smooth muscle cells and macrophages\textsuperscript{63–65)}
\item Induces ceramide accumulation in macrophages\textsuperscript{63)}
\end{itemize} \\
\hline
PGPC & & \begin{itemize}
\item Activates TRPA1-induced calcium influx\textsuperscript{81)}
\item Induces noncanonical and NLRP3 inflammasome activation in macrophages and DCs\textsuperscript{66)}
\item Inhibits LPS-induced noncanonical inflammasome activation in macrophages\textsuperscript{67)}
\item Induces apoptosis in smooth muscle cells and macrophages\textsuperscript{63–65)}
\item Induces ceramide accumulation in macrophages\textsuperscript{63)}
\end{itemize} \\
\hline
PEIPC & & \begin{itemize}
\item Induces adhesion molecules in endothelial cells by activating EP2 and DP\textsuperscript{83)}
\item Induces chemokines in endothelial cells\textsuperscript{46)}
\item Inhibits pro-inflammatory cytokines in bone marrow derived dendritic cells\textsuperscript{44)}
\end{itemize} \\
\hline
PECPC & & \begin{itemize}
\item Inhibits pro-inflammatory cytokines by covalent modification of cysteine residues in Keap1\textsuperscript{46)}
\item Induces chemokines in endothelial cells\textsuperscript{46)}
\item Inhibits pro-inflammatory cytokines in bone marrow derived dendritic cells\textsuperscript{44)}
\end{itemize} \\
\hline
HOOA-PC & & \begin{itemize}
\item High affinity ligand for CD36\textsuperscript{25)}
\item Reduces cathepsin B activity in macrophages\textsuperscript{66)}
\item Increases chemokines in endothelial cells\textsuperscript{46)}
\end{itemize} \\
\hline
KoDiA-PC & & \begin{itemize}
\item High affinity ligand for CD36\textsuperscript{25)}
\end{itemize} \\
\hline
Ether-linked PC (PAF-like lipid) & & \begin{itemize}
\item Induces Ca\textsuperscript{2+} influx into PMNs by binding to PAFR\textsuperscript{82)}
\item Induces NETs formation\textsuperscript{53)}
\item High affinity ligand for PPAR\textsuperscript{88)}
\item Induces CD36 expression\textsuperscript{88)}
\end{itemize} \\
\hline
PONPC & & \begin{itemize}
\item Enhances LPS stimulation in mouse alveolar macrophages\textsuperscript{40)}
\end{itemize} \\
\hline
\end{tabular}
\caption{Structures and Functions of Nonenzymatic OxPLs}
\end{table}
2-(oxo-nonanoyl)-sn-glycero-3-phosphocholine (PONPC), and 1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine (PAzPC) to be 1–3 µM in human atherosclerotic plaques and aortas of aged apoE−/− mice, whereas that in human and mouse plasma was 0.1–1 µM.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-

| Name         | Structure | Formation and function                                      |
|--------------|-----------|-------------------------------------------------------------|
| 5-HETE-PC    | ![Structure](image1.png) | • Produced by Alox5\(^{(31)}\)  
• Enhances thrombin generation\(^{(5,90)}\) |
| 12-HETE-PC   | ![Structure](image2.png) | • Produced by Alox12 or Alox15\(^{(34,38)}\)  
• Maintains immunologic tolerance in murine peritoneal macrophages\(^{(61)}\)  
• Facilitates autophagy\(^{(96)}\)  
• Enhances thrombin generation\(^{(5,90)}\)  
• Inhibits abdominal aortic aneurysm (AAA) development\(^{(42)}\)  
• Downregulated in Scott syndrome\(^{(35)}\) |
| 15-HETE-PC   | ![Structure](image3.png) | • Produced by Alox15\(^{(90)}\)  
• Enhances thrombin generation\(^{(5,90)}\)  
• Inhibits LPS-stimulated cytokine production in monocytes\(^{(20)}\)  
• Facilitates goblet cell differentiation\(^{(97)}\) |
| 15-HpETE-PE  | ![Structure](image4.png) | • Produced by Alox15\(^{(61)}\)  
• Upregulated in ferroptotic cells\(^{(61,84,93)}\)  
• Activates autophagy\(^{(96)}\)  
• Promotes cytokine expression through TLR4 activation\(^{(97)}\) |
| 14-HDoHE-PE  | ![Structure](image5.png) | • Produced by Alox12 or Alox15\(^{(32,38)}\)  
• Upregulated in platelets in response to thrombin\(^{(32)}\) |
| 17,18-EpETE-PL| ![Structure](image6.png) | • Produced by CYP\(^{(99)}\)  
• Modulates TRPV4 activity\(^{(65)}\) |
| PGE\(_2\)-PE  | ![Structure](image7.png) | • Produced by COX\(^{(34)}\)  
• Upregulated in platelets in response to thrombin\(^{(34)}\) |
| PGD\(_2\)-PE  | ![Structure](image8.png) | • Produced by COX\(^{(34)}\)  
• Upregulated in platelets in response to thrombin\(^{(34)}\) |
| DioxolaneA\(_3\)-PE | ![Structure](image9.png) | • Produced by COX\(^{(99)}\)  
• Upregulated in platelets in response to thrombin\(^{(99)}\)  
• Stimulates neutrophil integrin expression\(^{(99)}\) |
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.\(^{9}\) 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. Witzum 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.\(^{80}\)

Acknowledgments

This study was supported by the JSPS Grant-in-Aid for Scientific Research on Innovative Areas (KAKENHI 15H05897 and 15H05898 to M.A.), RIKEN Pioneering Project “Glyco-Lipidologue Initiative” (to M.A.), Keio Gijuku Academic Development Funds and Keio Gijuku Fukuzawa Memorial Fund for the Advancement of Education and Research (to R.A.).

Conflict of Interest

The authors declare no conflict of interest.
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