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Oxidative lipidomics: applications in critical care

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Abstract

Purpose of the review—Lipid peroxidation has long been established as a key player in the pathophysiology of critical care illnesses. Recent developments in oxidative lipidomics have aided in deciphering the molecular mechanisms of lipid oxidation. This review discusses the achievements and recent developments of oxidative lipidomics and its contribution to the understanding of critical illness.

Recent findings—Most studies involving acute injury focus on identifying the end products of lipid peroxidation. This misses the early events and targets of peroxidation mechanisms. Recent developments in LC-MS based oxidative lipidomics have enabled the identification of a wide variety of enzymatically generated lipid oxidation products both in clinical as well as animal injury models. Such lipid mediators have been found to play an important role in injury, inflammation, and recovery in disease states such as sepsis or head trauma.

Summary—Oxidative stress produces multiple lipid oxidation products either through enzymatic pathways or through free radical reactions. These products are often biologically active and can contribute to the regulation of cellular signaling. Oxidative lipidomics has contributed to the understanding of lipid peroxidation products, the mechanism of their production, time course of development after injury, and synergistic functioning with other regulatory processes in the body. These advances in knowledge will help guide the future development of interventions in critical illness.

Keywords

Poly unsaturated fatty acid (PUFA); Oxidized phospholipids; Liquid chromatography tandem mass spectrometry (LC-MS/MS); Specialized proresolving lipid mediators

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Introduction

Lipids represent a highly diverse group of cellular components that are known primarily as structural elements of the biological membranes as well as the storage of energy. However, the diversity of lipids and the huge number of proteins involved in lipid metabolism point to a functional role for them in cellular homeostasis. One such function is the production of specialized lipid mediators that signal or regulate various important events within the cell. The majority of lipid mediators are derived from oxidized lipids, particularly oxidized polyunsaturated fatty acids (PUFA), either in a free form or in an esterified form in phospholipids. Oxidative lipidomics, one of the latest fields to join the "-omics" arena, has improved the understanding of the role of oxidized lipids in cellular homeostasis as well as in disease pathologies. In the following sections, we will review the recent advancements in oxidative lipidomics methodologies and their role in understanding the contribution of oxidized lipids to critical illness.

Lipid peroxidation

Broadly speaking, lipid peroxidation can be defined as "insertion of a hyrodperoxy group into a lipid"[1]. Free and esterified (into phospholipids) PUFA are the primary targets of oxidation owing to the presence of an easily abstractable hydrogen atom located between the two double bonds. Lipid peroxidation can be triggered either by enzymatic or non-enzymatic reactions. Enzymes involved in lipid oxidation include lipoxygenases (LOX), cyclooxygenases (COX), and various cytochromes such as cytochrome p450 and cytochrome C. Non-enzymatic pathways mainly involve the formation of free radicals from the reaction of transition metals with reactive oxygen species through Haber-Weiss or Fenton's reaction. In either pathway, the lipid peroxidation involves initiation, propagation and termination [1]. The primary products formed are lipid-hydroperoxides (L-O-OH), which subsequently degrade into various secondary metabolites. [1] The (L-O-OH) and their secondary metabolites can function as signaling molecules [2].

Oxidative lipidomics

Lipidomics refers to the comprehensive analysis of lipids using analytical methods such as chromatography, nuclear magnetic resonance (NMR) and mass spectrometry (MS) [3,4]. Oxidative lipidomics is the recent addition to lipidomics that includes the structural, functional, and quantitative analysis of oxidatively modified lipids and their relationships to cellular signaling [5, 6].

Historically, oxidized lipids were identified through their end products via calorimetric assays, immunoassays, electron-spin-resonance, high performance liquid chromatography (HPLC), and gas chromatography–mass spectrometry (GC-MS) [7]. Current oxidative lipidomics methods mostly rely on liquid chromatography tandem mass spectrometry (LC-MS/MS) techniques. Oxidative lipidomics usually consists of four steps: 1) lipid extraction from fluid/tissue samples; 2) LC-MS/MS analysis; 3) data analysis; 4) integration of the obtained information into a biological system or disease mechanism.

While lipid extraction is well established, major advancements are happening in LC-MS/MS. Oxidized free fatty acids are mostly analyzed using targeted analysis in which a specific translational daughter ion formed in the fragmentation analysis (MS/MS) is monitored in parallel with the parent ion. Targeted analysis methods were established for 151 oxidized fatty acids [8**]. In human tears, targeted analysis was used to analyze 47 lipid mediators including an additional 22 not included in the aforementioned study [9**]. Our recent study which used a global oxidative lipidomics approach, showed 244 oxidized free fatty acids after trauma. However, we were only able to confirm the identity of 41 oxidized fatty acids using exact mass, fragmentation pattern, and retention time [10**]. This study not only indicated the presence of more oxidized fatty acids but also showed the need for novel comprehensive global analysis methods.

High throughput oxidative lipidomics can be challenging as many methods, including the above mentioned ones, require extensive sample preparation and clean-up. An improved LC-MS method that simplified the extraction and clean-up steps in a simple online column-switching HPLC setup demonstrated identification of 7 prostanoids directly from hepatocytes in a 96 well format [11*]. Similarly, a pilot study demonstrated the possibility of identifying degraded products of oxidized free fatty acids directly from exhaled breath in smokers in a high throughput manner [12*].

The analysis of oxidized phospholipids is complicated by their diversity. Using a lipidomics work flow that contained multiple chromatographic separations and in-house bioinformatics tools, Slater et al. identified 111 oxidized phospholipids in resting, thrombin-activated, and aspirinized platelets [13**]. More importantly, many of them were not previously identified and the structural details of these oxidized phospholipids were confirmed by fragmentation analysis. This study also identified three novel oxidized free fatty acids such as 14-hydroxynonadecatetraenoic, -trienoic and -dienoic acids [13**]. Using a simple chromatographic method, we identified 130 oxidized phospholipids from Pfa1 cells based on exact mass and retention time. This method also identified phospholipids containing di- and tri-hydroxyl PUFAs [14**, 15*]. To date, these two studies represent the highest number of identified oxidized phospholipids.

Following the recently developed nanoelectrospray direct-infusion mass-spectrometry-based metabolomics and lipidomics procedure [16], Taylor et al. developed a high-resolution, non-targeted, nanoelectrospray ionization (nESI) direct infusion mass spectrometry (DIMS). Based on the exact mass, the authors identified more than 100 oxidized lipids [17*]. Even though this method could be advantageous in terms of the time required for the analysis, inherent issues with the direct infusion make it likely that this method may still need optimization.

Despite criticisms [18*], colorimetric assays to measure the concentration of byproducts of lipid peroxidation such as thiobarbituric acid reactive substances are still used in assessing lipid peroxidation [19,20,21]. The calorimetric assays are nonspecific and do not provide quantitative information for *in vivo* measurements, however high sensitivity mass spectrometry methods for such analysis are being developed [22]. Another lipid peroxidation end product 4-hydroxynanoenol (4-HNE) often covalently attaches to proteins and thereby

alters cellular functioning. HNE modified proteins are identified by calorimetric and immunological methods. Recently targeted proteolipidomics strategies have also been developed for the detection of 4-HNE modified proteins [23, 24*].

Oxidative lipidomics in critical illness and related pathophysiological pathways

Disturbances in cellular redox status are often involved in the pathophysiology of many critical illnesses such as sepsis, trauma, ischemia reperfusion, and other acute injuries. Oxidative lipidomics led to a paradigm shift in this field as it established the role of oxidized lipids as mediators of the body's response to injury.

Sepsis and shock are manifested by a deluge of inflammatory responses. A variety of oxidatively modified free fatty acids such as prostaglandins, hydroxyl, and dihydroxyl fatty acids are generated in such responses [25]. Oxidative lipidomics has contributed to this field by providing a system-level approach in understanding the precise balance between the mediators and their effects in modulating inflammatory processes. Analysis of the production of 141 lipid mediators upon infection of mice with influenza viruses of varying virulence showed a correlation of 5-LOX products with the inflammatory process and 12/15-LOX products with the resolving phase of inflammation [26]. The ratio of two linoleic acid oxidation products, 9- hydroxyoctadecadienoic acid (HODE) and 13-HODE, was reported to be a marker of pro and anti-inflammatory stages. This finding was also confirmed in a similar analysis in nasopharyngeal lavages of humans infected with influenza virus [26]. Similar oxidative lipidomic profiling of peripheral blood mononuclear cells isolated from moderate to severe asthmatics that were treated with low molecular weight hyaluronan (generated through tissue injury or inflammation, accumulates in the asthmatic lung and serum, and correlates with disease severity) provided new evidence of the connection between inflammatory mediators and extracellular milieu [13**].

Oxidative lipidomics enables the identification of novel lipid mediators and their synthesis in the inflammatory process. Recently, 8-hydroxy-9, 11-dioxolane eicosatetraenoic acid (dioxolane A3, DXA3) was identified in thrombin-activated platelets [27*]. Lipidomics analysis also established the formation of eicosanoid-lysolipids from 2-arachidonoyl-lysolipids by COX-2 and the release of eicosanoids from eicosanoid-lysolipid precursors by intracellular lipases (particularly, iPLA2γ) [28*]. Specialized proresolving mediators (SPMs) are a group of lipid mediators that have been identified with the aid of oxidative lipidomics. This group consists of lipid mediators such as lipoxins (LX), protectins (PD), maresins (MaR), and resolvins (RV) which are involved in the resolution phase of sepsis. Two maresins that are involved in the resolution of inflammation, 22-hydroxy-MaR1 and 14-oxo-MaR1, were recently identified in *Escherichia coli* infectious exudates and added to this group of SPMs [29*].

Not only has oxidative lipidomics aided in the identification of new lipid mediators, these techniques have also allowed the study of the underlying mechanism in lipid-mediated cellular signaling. Resolvin-D2 has been found to act via the cell surface G protein-coupled receptor (GPR18/DRV2), CREB, ERK1/2, and STAT3 signaling pathways [30*]. The

response of conjunctival goblet cells to LXA4, was found to occur through the ALX/FPR2 receptor mediated pathway [31]. Furthermore, analysis of human milk showed multiple SPMs such as RvD1, RvD2, RvD3, AT-RvD3, RvD4, PD1, MaR1, RvE1, RvE2, RvE3, LXA4, and LXB4 indicating potential maternal-infant biochemical imprinting towards the body's response to infection and inflammation [32*].

The development of precise oxidative lipidomics methods have also been integrated into applied studies. A detailed comprehensive lipid mediator study in two models of sepsis induced by LPS and cecal ligation and puncture (CLP) reported a 2100% and 97% increase in prostaglandin-E2, respectively. Plasma oxylipin levels including epoxy-, hydroxyl-, and dihydroxy-fatty acids were significantly elevated in both models. This study also showed an organ-specific increase in selected oxidized free fatty acids after sepsis [33**]. In a mouse poly-microbial sepsis model, exposure of mesenchymal stromal cells to carbon monoxide improved therapeutic efficacy partially through promoting SPM production. These results shows the importance of SPMs in treating sepsis [34*]. In a different set of experiments with a similar sepsis model, NLRP3 inflammasome deficiency protected against sepsis by downregulating pro-inflammatory lipid mediators and upregulating SPMs, particularly through the increased synthesis of the arachidonic acid-derived lipid mediator, lipoxin B4 [35*]. Along these lines, a lipid mediator study in medical ICU patients with sepsis showed higher pro- inflammatory mediators such as prostaglandin F2α and leukotriene B4 in non-survivors and higher proresolving mediators such as resolvin E1, resolvin D5, and 17R-protectin D1 in survivors [36**]. Oxidative lipidomics combined with bioassays on cultured bovine pulmonary artery endothelial cells (BPAECs) suggested that oxidized cardiolipin species may be hydrolyzed by iPLAγ2 to produce mono- and di-lysoCL which along with 9- and 13- HODE may lead to impaired function of the pulmonary endothelial barrier function as well as necrosis [37]. Lipid mediators and their pathways can also be disrupted by interactions with pathogens. The lungs of cystic fibrosis patients with recurrent *Pseudomonas aeruginosa* infection often represent a chronic hyper-inflammatory environment. Detailed lipid mediator analyses indicate that this pathogen secretes cystic fibrosis transmembrane conductance regulator inhibitory factor (Cif) which hydrolyzes 14,15-epoxyeicosatrienoic acid, thereby inhibiting the production of the proresolving lipid mediator 15-epi lipoxin A4 [38*].

Similar to oxidized free fatty acids, oxidized esterified fatty acids such as oxidized phospholipids (PLs) are involved in the inflammatory process. Oxidized phospholipids are now recognized as damage associated molecular patterns (DAMPs) and their pattern recognizing receptors (PRR) in signaling have been identified [39*]. Results from multiple studies have shown that oxidized PLs possess a pleotropic action of pro- and anti-inflammatory functions and a balanced, harmonious action of oxidized phospholipids are necessary in the clearance of infection. In a heat-killed *Staphylococcus aureus* bacterial infection model, posttreatment with oxidized phosphatidylcholine dramatically accelerated lung recovery by restoring lung barrier properties [40]. Elevated amounts of oxidized phospholipids including mono- and di-oxygenated cardiolipin species were found in the lungs of the mice infected with *Klebsiella pneumoniae* [41]. A novel phospholipid oxidation product from 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PAPC), deoxy-A2/J2-isoprostanes-phosphocholine (deoxy-A2/J2-IsoP-PC), was identified and determined

to have an anti-inflammatory role [42*]. In activated platelets, an eicosanoid (DXA_3) attaches to phosphatidylethanolamine to form esterified eicosanoids which activate the expression of neutrophil integrins [43*].

Lipid peroxidation has been extensively studied and has been identified as a major pathophysiological event after traumatic brain injury (TBI). Although the end products of lipid peroxidation after TBI have been established, the actual lipid species that undergo peroxidation were not identified until the advent of oxidative lipidomics. In our oxidative lipidomics analysis, we found that the major oxidized phospholipids early after TBI are cardiolipin and phosphatidylserine [44]. Oxidized cardiolipins are then hydrolyzed in the mitochondria through calcium independent phospholipase A2 to produce a plethora of oxidized lipid mediators [45]. Using a global free fatty acid analysis of the brain lipidome, we identified 244 distinct oxidized free fatty acid species after experimental controlled cortical impact (CCI) in rats. The results indicated a predominance of enzymatic lipid peroxidation after the injury in addition to a differential time course of pro- and anti-inflammatory oxidized free fatty acids. Both the pro- and anti-inflammatory lipid mediators were synthesized and peaked at 1h after injury, the pro-inflammatory mediators cleared by 24h, but the anti-inflammatory, proresolving mediators such as neuroprotectin D1, protectin DX1, resolvin D5, and resolvin D1 remained elevated until 24h following the CCI [10**].

Lipid peroxidation is the major event involved in ferroptosis, a specific cell death pathway implicated in critical illnesses such as acute renal injury. Thorough mining of oxidative lipidomics analysis from cells undergoing ferroptosis revealed oxidized arachidonic and adrenic acid containing phosphatidylethanolamines (PE) as ferroptotic navigators [14,15]. Detailed structural analysis further narrowed down these mediators to di- or tri-oxygenated arachidonic and adrenic acid-containing PE species. This connects the specific role of different players in ferroptosis, such as glutathione peroxidase4 (GPX4) (lipid hydroperoxide reductase; inhibits ferroptosis) acyl CoA synthetase long-chain family member-4 (ACSL4) involved in esterification of arachidonic and adrenic acids into PL; positively regulates ferroptosis). Moreover, these results highlight the usefulness of oxidative lipidomics in precisely decoding a complex cell death pathway which may aid in the design of targeted therapies in the future.

The deeper understanding of lipid peroxidation that has been made possible by oxidative lipidomics has also emphasized the fact that lipid peroxidation is a highly complex phenomena. This has necessitated *in silico* analysis of lipid mediator pathways as demonstrated by Gupta et al., who used existing oxidative lipidomic knowledge to model the molecular mechanisms of ω-3 and ω-6 lipid peroxidation in mammalian cells [46**] and by our use of phospholipid oxidation data to model the ferroptotic network [14].

Conclusion and future scope

Oxidative lipidomics has enabled the identification of various lipid oxidation products and the improved understanding of their pathophysiological functioning. However, this powerful technique is still in its infancy. The number of identified oxidized lipids is negligible compared to the total possible number that can be generated from known lipid structures.

The biggest limitation of oxidative lipidomics is this inability to identify and quantify all oxidized lipids. Given that oxidized lipids often activate metabolic pathways, they are usually present in very low quantities. Analysis of low-abundance, oxidized lipids in the presence of high-abundance, non-oxidized structural lipids is a daunting task. This requires very specific and sensitive methods including powerful robust software packages and a definitive oxidized lipid database. Nevertheless, oxidative lipidomics has begun to decode the complex mechanisms behind lipid peroxidation and its relationship to critical illness. Understanding the role of lipid mediators in different phases of injury or healing is important for selecting therapeutic targets. Interactions of lipid mediators with other molecules and the increasing availability of compounds that can inhibit their functions will help facilitate the design and development of new targeted therapies.

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Key points

- Oxidative lipidomics refers to structural, functional, and quantitative analysis of oxidatively modified lipids and their relationships to cellular signaling
- Oxidative lipidomics identified various lipid mediator and pathological pathways in critical illness
- Precise identification of mediators involved in cell death pathway is possible with oxidative lipidomics.