This is the Introduction to a thematic series on Lipid Oxidation and Cardiovascular Disease, which includes the following articles:

**Lipid Oxidation and Cardiovascular Disease: Introduction to a Review Series**

- Novel Lipid Mediators Promote Resolution of Acute Inflammation: Impact of Aspirin and Statins
- Oxidation-Specific Epitopes Are Danger-Associated Molecular Patterns Recognized by Pattern Recognition Receptors of Innate Immunity
- Aldehydic Lipid Peroxidation Products and Cardiovascular Disease
- Phospholipid Oxidation Products in Cardiovascular Disease
- Isoprostanes as Biomarkers and Effectors in Cardiovascular Disease

_Stan Hazen and Thomas M. McIntyre, Guest Editors_

**Lipid Oxidation and Cardiovascular Disease: Introduction to a Review Series**

Thomas M. McIntyre, Stanley L. Hazen

Atherosclerosis and the associated adverse complications of cardiovascular disease are major causes of morbidity and mortality in people living a Western lifestyle. A role for excess cholesterol in the pathophysiology of atherosclerosis is clear. However, additional mechanisms driving the relevant pathological changes in a chronic disease such as atherosclerosis are those that constitute the acute inflammatory response. The essential elements of a physiological, and regulated, inflammatory response starts with stimulated endothelium, displaying adhesive molecules for circulating white blood cells. This is accompanied by localized production of cell type–specific agonists for adherent monocytes, neutrophils, or lymphocytes by the activated endothelium. These agonists then activate the migratory instruction set of adherent or rolling cells positioned to receive both adhesion- and agonist-related stimuli from activated vascular endothelial cells. Lipid oxidation products formed by virtually every vascular cell type participate in orchestrating these processes. We also have recently come to appreciate that the inflammatory process is actively limited by activation of a resolution phase, often via generation of structurally specific oxidized lipids whose function is to orchestrate resolution of inflammation. The overall goal of this review series is to place recent observations and insights in rapidly developing areas of lipid oxidation into the framework of cardiovascular disease.

Enzymatic and free radical oxidation have prominent roles in cardiovascular disease through their oxidative modification of existing molecules. Lipids are primary targets of this modification because they are the primary repository of oxidizable olefinic or double bonds. Oxidized lipids are best understood as oxygenated arachidonic acid products, the prostaglandins, leukotrienes, and thromboxane A₂, that have diverse and potent effects throughout the inflammatory and reparative responses. These oxidized lipid mediators are well understood. Phospholipid oxidation products are more recent additions to the family of inflammatory, regulatory, and pathological lipid. Accordingly, the activities of these lipids have yet to be fully elucidated, although recent progress has at least identified the structures of many biologically or chemically reactive phospholipid oxidation products.

Polyunsaturated fatty acids, that is, those with more than a single double bond, are prone to chemical and enzymatic oxidation, the same chemical processes involved in making butter rancid. The basis for this susceptibility is that the hydrogen decorating the carbon atom between 2 adjacent...
double bonds (double bonds of biologically relevant fatty acids are always separated by a single –CH2– group) is the weakest bond in the fatty acid or fatty acyl chain if the fatty acid is esterified in a complex phospholipid. Activated inflammatory cells generate chemically reactive oxygen species and produce enzymes, eg, myeloperoxidase, that can initiate lipid peroxidation via generation of reactive oxidants that abstract this weakly bound hydrogen.7 Bond rearrangement ensues, molecular oxygen may be adducted, and the rate of bond cleavage is greatly increased in this unstable state until the molecule is stabilized. This form of chemical reaction, acting through free radicals, is unrestricted by rules that govern those that control most of our metabolic changes, with the result being that oxidative attack on polyunsaturated fatty acids and phospholipids that contain them produces a plethora of reaction products.8

The present series of review articles in Circulation Research will address numerous facets of lipid oxidation, generation of biologically active species, and their involvement in cardiovascular and inflammatory disease processes. One of the reviews will explore the role of a subset of these species, the isoprostanes, as effectors of cardiovascular disease. Directed oxidation by cell-specific oxygenases form the eicosanoid family of signaling molecules,9 but this limited pool of oxidation products is greatly expanded by nonenzymatic oxidation. Unrestricted chemical attack on arachidonic acid, with its 20 carbon atoms and 4 double bonds, generates a mix of all possible positional and stereoisomers (64 in all). Dr Roberts explores the biological role of these homologs of enzymatic reactions, the isoprostanes, and shows how these structures formed only by chemical oxidation are premier, and indeed exclusive, reporters of endogenous oxidative stress and mechanistically linked to vascular function. This synopsis will be presented in “Isoprostanes as Biomarkers and Effectors in Cardiovascular Disease.”

Another class of reactive lipid oxidation products arising from oxidative attack on polyunsaturated fatty acids are oxidative fragments of the fatty acid chain with newly introduced aldehydic functions (where the carbon chain terminates with a C==O function). Some of these products additionally retain a double bond, which, because of the preceding bond rearrangement, makes them highly reactive α, β unsaturated aldehydes (so called “-enals”). These electrophilic species readily covalently modify nucleophilic groups on target proteins. They also extensively derivatize thiol groups on target proteins. They also extensively derivatize reduced glutathione, thereby decreasing cellular antioxidant protection. This area is the subject of the upcoming review in this series entitled “Aldehydic Lipid Peroxidation Products and Cardiovascular Disease” by Dr Sanjay Srivastava.

Chemically reactive functions also are found in the complex lipids that come out of the crucible of polyunsaturated phospholipid oxidation. These aldehydic phospholipids can form stable protein adducts, which are premier markers of tissue oxidative damage. Some of these lipid–protein adducts form oxidation-specific neoepitopes that promote and provoke an immune response to structures present in atherosclerotic lesions. Indeed, this class of neoepitopes appear to be dominant targets of the innate immune system and have major roles in recognition and clearance of apoptotic cells and cellular debris. Drs Yury Miller, Joseph Witztum, and others will review this broad area in the upcoming article in this series “Oxidation-Specific Epitopes Are Danger-Associated Molecular Patterns Recognized by Pattern Recognition Receptors of Innate Immunity.”

Phospholipid composition is diverse, and unrestricted oxidation makes the pool more so. As cellular membranes undergo lipid peroxidation, such as during senescence, apoptosis, or at sites of inflammation, previously hydrophobic portions of fatty acids become more polar and move from the interior of the lipid bilayer to the aqueous membrane surface. This facilitates physical contact between pattern recognition receptor and molecular pattern ligand. Oxidized cell membranes and lipoproteins thus display on their surface a chemical Braille that can encode signals from phospholipids that have undergone peroxidation, with many of their oxidized fatty acids protruding at the surface (also known as the “lipid whisker” model).9 Some of these oxidation products are biologically active, stimulating a range of responses. For example, many oxidatively truncated phospholipid oxidation products serve as ligands for the prototypical inflammatory receptor for platelet-activating factor (PAF).11 Some of the structurally specific oxidized phospholipids that serve as PAF-like mediators can readily enter cells to stimulate nuclear hormone receptors, whereas others disrupt mitochondrial function to initiate the intrinsic apoptotic caspase cascade. A distinct structural class of oxidatively cleaved phospholipids serves as high-affinity ligands and agonists for the scavenger receptor CD36, triggering macrophage foam cell formation, enhanced platelet hyperresponsiveness and a prothrombotic phenotype.12,13 S.L.H. and T.M.M. will review the lipid whisker model of oxidized phospholipids, as well as a host of biologically active phospholipids linked to atherothrombotic heart disease, in the upcoming article in this series “Phospholipid Oxidation Products in Cardiovascular Disease.”

We now appreciate that resolution of inflammatory signaling events is an active process and is regulated by distinct isomers of arachidonic, docosahexaenoic, and eicosapentaenoic acid oxidation products. In this issue of Circulation Research, the article “Novel Lipid Mediators Promote Resolution of Acute Inflammation: Impact of Aspirin and Statins” by Drs Matthew Spite and Charles Serhan comprehensively reviews the classes of lipoxins, resolvins, protectins, neuroprotectins, and the newly discovered maresins.14 Although disregulated resolution may promote atherogenesis, success with synthetic proresolving lipid mediators offers the promise of direct intervention in chronic inflammatory diseases such as atherosclerosis. In the first article of the review series on oxidized lipids, Drs Spite and Serhan review the structure, biosynthesis, and proresolving functions of various endogenous oxidized lipids. The protective roles of these novel lipid mediators, and their relationships to both aspirin use and pleiotropic actions of statin therapy, are discussed.

Sources of Funding
Supported by NIH grant P01HL087018 (to T.M.M. and S.L.H.).

Disclosures
None.
References


Key Words: free radicals [lipid metabolites] oxidative stress [oxidized low-density lipoprotein] reactive oxygen species
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_Circ Res._ 2010;107:1167-1169
doi: 10.1161/CIRCRESAHA.110.224618
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/107/10/1167

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