Trends in Endocrinology & Metabolism

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Review

Context-Dependent Role of Oxidized Lipids and Lipoproteins in Inflammation

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Oxidized low-density lipoprotein (OxLDL), which contains hundreds of different oxidized lipid molecules, is a hallmark of hyperlipidemia and atherosclerosis. The same oxidized lipids found in OxLDL are also formed in apoptotic cells, and are present in tissues as well as in the circulation under pathological conditions. In many disease contexts, oxidized lipids constitute damage signals, or patterns, that activate pattern-recognition receptors (PRRs) and significantly contribute to inflammation. Here, we review recent discoveries and emerging trends in the field of oxidized lipids and the regulation of inflammation, focusing on oxidation products of polyunsaturated fatty acids esterified into cholesteryl esters (CEs) and phospholipids (PLs). We also highlight context-dependent activation and biased agonism of Toll-like receptor-4 (TLR4) and the NLRP3 inflammasome, among other signaling pathways activated by oxidized lipids.

Complexity of OxLDL

A PubMed search for oxidized low-density lipoprotein (**OxLDL** (see Glossary) yields between 6000 and 9000 papers, depending on spelling. These publications refer to OxLDL as a complex lipoprotein comprising approximately 600 molecules of unesterified (free) cholesterol (FC), 1600 cholesteryl esters (Es), 700 phospholipids (PLs), 185 triglycerides (TGs), and one molecule of apolipoprotein B-100 (apoB). CE, PL, and TG are all esters incorporating one, two, or three fatty acyl chains, respectively. Among the variety of saturated and nonsaturated fatty acyls, linoleic (LA), arachidonic (AA), and docosahexaenoic (DHA) acids are common polyunsaturated fatty acyls (PUFA) in these esters.

Cholesterol and PUFA are susceptible to enzymatic and free radical oxidation, producing hundreds of oxidative products. Furthermore, OxCE and OxPL can covalently modify apoB and other proteins; can be hydrolyzed by lipases to produce oxidized free fatty acids; and can decompose to produce highly reactive end-products, such as malondialdehyde (MDA) or 4-hydroxy-2-nonenal (4-HNE), which in turn covalently modify proteins and some PLs [1]. This partial list underscores the complex composition of OxLDL.

Evidently, all of these products are unlikely to occur in one OxLDL particle simultaneously, which would otherwise require a prolonged incubation of native LDL with ions of transition metals (e.g., copper). Examples of a more 'physiological' model of OxLDL are made from LDL *in vitro* with cells overexpressing 15-lipoxygenase (15-LO), incubated with myeloperoxidase, hemoglobin, or free radical generators [2,3]. The important fact is that, regardless of the *in vitro* model, many of the oxidized lipid species found in OxLDL have also been found in human blood, atherosclerotic lesions, inflamed lung, multiple sclerosis brain, and rheumatoid joints, to mention only a few from the long list of pathological conditions and associated tissues [4–7].

Trends

Lipoprotein and intracellular lipid oxidation is a common pathophysiological response to oxidative stress and hyperlipidemia.

Oxidized lipids and lipoproteins, acting as damage-associated molecular patterns (DAMPs), activate pattern-recognition receptors (PRRs) and induce transcription factor- and NLRP3 inflammasome-mediated immune responses in macrophages and endothelial cells. Such induction can have either adverse or protective effects depending on time, tissue, and pathophysiological context.

Innate immune responses to oxidized lipid DAMPs often differ from those to microbial pathogen-associated molecular patterns (PAMPs), representing biased agonism of PRRs.

Retention of oxidized lipoproteins in the vessel wall synergizes with injury to the endothelium to promote atherogenesis. These data effectively merge the 'response-to-retention' and 'response-to-injury' hypotheses.

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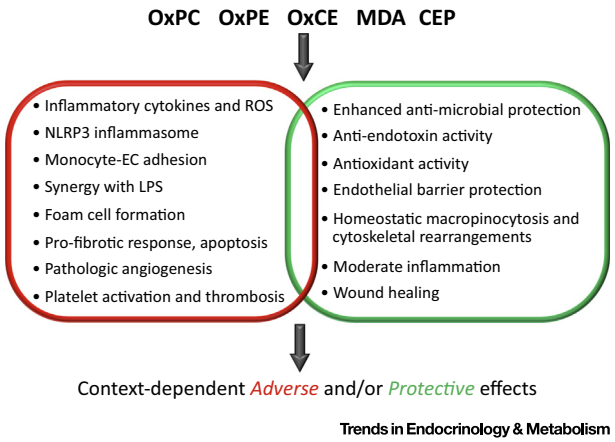

Figure 1. Context-Dependent Adverse and Protective Effects of Oxidized Lipids. This chart summarizes, in an abbreviated format, the major adverse and protective effects of key oxidized lipids reviewed in this article. It also emphasizes that a specific cellular response to oxidized lipids can have adverse and/or protective effects, depending on the tissue and pathology context. Abbreviations: CEP, 2-(ω-carboxyethyl)pyrrole [oxidation end-product of docosahexaenoic acid (DHA)]; MDA, malondialdehyde [including MDA derivatives, such as malondialdehyde-acetaldehyde (MAA)]; OxCE, oxidized cholesteryl ester; OxPC, oxidized phosphatidylcholine; OxPE, oxidized phosphatidylethanolamine.

Part of the reason for this widespread occurrence of oxidized lipids and their covalent adducts to proteins is that they arise not only in LDL (and high-density lipoprotein; HDL) as a consequence of an oxidative insult, but also in cells, intracellularly and on the cell surface, both under physiological conditions and particularly under stress and during apoptosis.

The DAMP Concept

Oxidized lipids and lipoproteins exert profound biological effects, both homeostatic and adverse, depending on duration and tissue context. This is often explained as due to the formation of **damage-associated molecular patterns** (DAMPs) arising from the oxidative damage of lipids and lipoproteins [4,8]. Host-derived DAMPs share common structural motifs with microbial **pathogen-associated molecular patterns** (PAMPs) and/or activate the same pattern-recognition receptors (**PRRs**) present on immune and vascular cells.

The phosphocholine (PC) epitope is one such example. PC is the most common head-group of PLs and is not recognized by any PRR in native LDL or on the surface of viable cells. However, an exposed PC of OxPL, such as POVPC [1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine], in OxLDL and on apoptotic cells is a major ligand that mediates the binding of OxLDL to CD36 and scavenger receptor class B type I (SR-B1). CD36 recognizes the PC on both free POVPC and POVPC covalently linked to apoB, as does the soluble PRR natural antibody E06/T15 [9–12]. These properties make host-derived PC in OxPL, but not in nonoxidized PL, a DAMP. The same PC group is an exposed moiety on the cell wall polysaccharide of common infectious pathogens, including pneumococci, which makes bacterial PC a PAMP. Immunizing *Ldlr*$^{-/-}$mice with *Streptococcus pneumoniae* raised E06/T15 titers and protected mice from diet-induced atherosclerosis, the pathology in which OxPL has a major role [13].

The concept of DAMPs and PAMPs activating the same PRRs implies that the end result of this activation would be similar, if not the same. However, this is not always the case. In the mechanisms described below, we emphasize not only similarities, but also the differences and bias in PRR activation by DAMPs compared with PAMPs. We also describe both adverse and protective effects of oxidized lipids occurring in different tissue and pathophysiological contexts (Figure 1).

Biased Activation of TLR4 by OxCE and OxPE versus LPS in Macrophages

Oxidized CEs (OxCEs) have been identified as active components in the OxLDL produced by LDL incubation with cells expressing 15-LO [14–16]. Unlike an OxLDL oxidized with Cu^{2+}, the

Glossary

Biased agonism: also known as 'functional selectivity'; refers to the binding of different ligands to the same receptor but activating distinct signaling pathways.

Damage-associated molecular patterns (DAMPs): the term was introduced by analogy to PAMPs and refers to host-derived biomolecules that, upon modification, often oxidation, become agonists to the same PRRs that are activated by PAMPs.

Inflammasome: a key component of the innate immune system. Induced and activated by PAMPs and DAMPs, the inflammasome component proteins NLRP3, ASC, and procaspase-1 form a high-order complex, leading to the sequential cleavage and activation of caspase-1 and IL-1β.

Oxidized cholesteryl ester (OxCE): often created by oxidation of cholesteryl arachidonate with 15-lipoxygenase or a free radical generator. For the purpose of this article, OxCE refers to CE molecules with an oxidized PUFA acyl chain, but not oxidized cholesterol.

Oxidized low-density lipoprotein (OxLDL): an *in vitro* model of OxLDL is often achieved by incubating native LDL with Cu^{2+}. This robust free radical oxidation reaction yields many OxPL, OxCE, oxysterol, and end oxidation products. Other methods to oxidize LDL can produce a more limited set of oxidation products. The presence of many of the same oxidized lipid species, as generated in OxLDL, in human plasma and atherosclerotic lesions supports the importance of the OxLDL model.

Oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (OxPAPC): often created by exposure of PAPC to air; this is a common model of oxidized PLs, comprising tens of oxidative products, some of which are described in this review.

Pathogen-associated molecular patterns (PAMPs): the concept of PAMPs helps explain how structurally different molecules of different pathogens activate the same PRRs of the innate immunity, such as Toll-like and scavenger receptors.

Sterol regulatory element-binding protein 2 (SREBP2): a transcription factor governing cholesterol homeostasis by transactivating genes