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Review

Hormetic and anti-inflammatory properties of oxidized phospholipids

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ABSTRACT

Oxidized phospholipids are generally recognized as deleterious factors involved in disease pathogenesis. This review summarizes the data suggesting that under certain biological conditions the opposite is correct, namely that OxPLs can also induce protective effects. Examples that are discussed in the review include upregulation of antioxidant genes, inhibition of inflammatory signaling pathways through Nrf2-dependent and -independent mechanisms, antagonism of Toll-like receptors, immuno-modulating and immunosuppressive action of OxPLs in adaptive immunity and autoimmune disease, activation of PPARs known for their anti-inflammatory action, as well as protective action against lung edema in acute lung inflammation. The data support the notion that oxidation of phospholipids provides a negative feedback preventing damage to host tissues due to uncontrolled inflammation and oxidative stress.

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1. Introduction

It is generally accepted that oxidized lipids that are produced as a result of uncontrolled non-enzymatic oxidation demonstrate predominantly toxic and pro-inflammatory activities and are important pathogenic factors in a variety of

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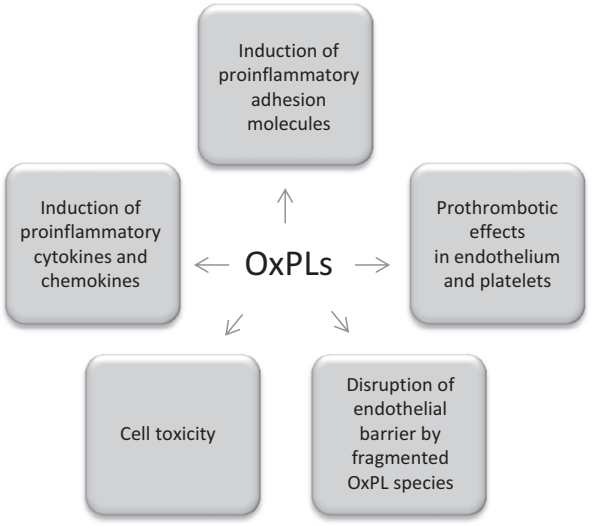

Fig. 1. Some pathological properties of OxPLs. OxPLs induce proinflammatory reactions via upregulation of cell adhesion molecules, cytokines and chemokines. Additionally, exposure of cells to OxPLs causes prothrombotic and toxic effects. In addition, oxidatively fragmented PLs were shown to disrupt lung endothelial barrier.

diseases. This review is dedicated to oxidized phospholipids (OxPLs), which are formed both by enzymatic and non-enzymatic mechanisms. Biological activity of these lipids was first convincingly described in 1997 in a seminal paper by Berliner's group, who isolated representative molecular species of OxPLs and demonstrated their pro-inflammatory activity in endothelial cells (Watson et al., 1997). Since then dozens or even hundreds of papers were published describing negative roles of OxPLs in a variety of pathological states and implicating these lipids as culprits in acute and chronic inflammation (Fig. 1). However, some works described biological activities that did not fit this negative characteristic because such effects are generally regarded as tissue-protective and anti-inflammatory. In this review we focused on such potentially beneficial effects of OxPLs that gained less attention in recent reviews (Aldrovandi and O'Donnell, 2013; Lee et al., 2012; Matt et al., 2014; Salomon, 2012; Stemmer and Hermetter, 2012) as compared to pro-inflammatory species. The purpose of such a "biased" review is to provide readers with a broader and more balanced view of "good" and "bad" sides of OxPLs action in oxidative stress and inflammation.

2. Formation, structure and catabolism of OxPLs

Glycerophospholipids (PL) are natural compounds consisting of a glycerol backbone with fatty acids (FAs) at its first and second positions and a phosphodiester polar head group at the third. The second position in PLs is usually occupied by an unsaturated FA with one or more double bonds. Similarly to free unesterified FAs, such unsaturated FAs within PLs are prone to oxidation with formation of OxPLs either enzymatically or non-enzymatically.

OxPLs can be generated by three mechanisms. First, PL-esterified polyunsaturated fatty acids (PUFAs) are highly prone to oxidation because reactive oxygen species can easily abstract hydrogens from methylene groups between the double bonds and therefore initiate the addition of oxygen molecules leading to formation of peroxyl radicals, which are quickly transformed to their more stable derivatives – hydroperoxides or hydroxides. These compounds can acquire additional oxygen atoms and undergo rearrangements, cyclization and/or fragmentation (Fig. 2A) (Bochkov et al., 2010; Reis and Spickett, 2012). The second pathway initiating oxidation of PUFA-containing PLs is an enzymatic transformation by certain types of lipoxygenases (LOX). From all known lipoxygenases only members of the 12/15-LOX family are able to directly oxidize PL-esterified PUFAs (Ivanov et al., 2015; Kuhn et al., 2015). The common product of such peroxidation is a monohydroperoxide, which is usually quickly reduced by cellular enzymes to a monohydroxide. Such PL-esterified residues can undergo further non-enzymatic oxidation, rearrangements, cyclization and fragmentation (Fig. 2A). The third mechanism producing OxPLs (Fig. 2B) begins from oxidation of free, unesterified PUFAs either by lipoxygenases (12- or 5-LOX) or cyclooxygenase-1, which is followed by reesterification to form OxPLs (Aldrovandi et al., 2013; Clark et al., 2011; Morgan et al., 2010). The mechanisms and importance of the reesterification pathway are currently under investigation.

As a result of lipid peroxidation dozens of different molecular species can be formed from one individual precursor. All OxPLs can be divided into non-fragmented and fragmented species, which contain either full chain of carbon atoms, or oxidatively truncated chain (Fig. 3). The diversity of generated OxPLs is explained by presence of different oxygen-containing functional groups and their combinations: hydroxy-, hydroperoxy-, epoxy-, keto-groups within the residue or aldehyde or carboxylic groups at the omega-end of a fragmented residue. Both fragmented and non-fragmented OxPL-residues can be chemically inert or reactive. High reactivity is characteristic of aldehyde, epoxy- or keto groups especially in combination with unsaturation in close proximity to these functional groups. Highly reactive electrophilic compounds, for example α, β-unsaturated hydroxyalkenals, are able to covalently modify thiol and amino-groups of biomolecules and therefore have prominent influence on multiple cellular activities as discussed below in this review.

OxPLs do not accumulate *in vivo* under normal conditions, suggesting that in normal tissues they are rapidly removed. OxPLs can be catabolized by two mechanisms: degradation or detoxification. Several enzymes have been shown to catalyze cleavage of OxPLs. Plasma platelet-activating-factor-acetylhydrolase (Stremler et al., 1989) and intracellular platelet-activating-factor-acetylhydrolase (PAF-AH) of type II (Hattori et al., 1993) hydrolyze both fragmented short-chain OxPLs (1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine (POVPC), 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine (PGPC), *etc.*) and non-fragmented OxPLs, e.g., isoprostane-containing OxPLs (1-palmitoyl-2-(5,6-epoxyisoprostane E2)-*sn*-glycero-3-phosphocholine (PEIPC)) (Stafforini et al., 2006). The former is a preferred substrate as compared to isoprostane-containing OxPLs (Stafforini et al., 2006). As a result of OxPLs' cleavage at *sn*-2 position, lyso-PLs and free oxidized fatty acids (OxFAs) is formed.

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