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Forum Review

Apoptotic Cells as Sources for Biologically Active Oxidized Phospholipids

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ABSTRACT

Acute inflammation is characterized by an accumulation of polymorphonuclear cells (PMNs), generation of reactive oxygen species, subsequent apoptosis of PMNs, and finally phagocytosis of apoptotic cells by macrophages. Recently, it has been demonstrated that during apoptosis oxidation of membrane phospholipids, especially phosphatidylserine, occurs. Moreover, we have shown that membrane vesicles released from apoptotic cells contain biologically active oxidized phospholipids. The involvement of oxidized phospholipids in the development of atherosclerosis, which is described as a chronic inflammatory disease, is increasingly recognized. These oxidized phospholipids were shown to induce several proinflammatory genes, such as monocyte chemoattractant protein 1 or interleukin-8, and it is hypothesized that lipid oxidation products also play a role in other chronic inflammatory disorders. On the other hand, oxidized phospholipids were shown to exert antiendotoxin effects by inhibiting lipopolysaccharide-induced signaling, representing a possible feedback loop during gram-negative infection. Additionally, it has been described that oxidized phospholipids are capable of inducing genes such as heme oxygenase-1 that are important for the resolution of acute inflammation. Moreover, oxidized phospholipids serve as recognition signals on apoptotic cells facilitating phagocytosis. In this review, we discuss the hypothesis that oxidized phospholipids generated in apoptotic cells (a) propagate chronic inflammation and (b) contribute to the resolution of acute inflammation. *Antioxid. Redox Signal.* 6, 311–320.

INTRODUCTION

INFLAMMATION is a protective response to challenging microorganisms or tissue damage that finally leads to tissue repair and restoration of tissue function. Under normal conditions, inflammatory processes are self-limiting, resulting in complete resolution without loss of tissue function. Such inflammatory reactions involve the sequential release of pro- and antiinflammatory mediators, increase of microvascular permeability, and exudation of fluid and plasma proteins into the inflamed tissue. In the early (acute) phase of inflammation, polymorphonuclear leukocytes (PMNs) are predominant. PMNs are rapidly recruited to the site of infection or injury and thus build the first line of defense against invading microorganisms. After activation by bacterial products or inflammatory cytokines, PMNs generate reactive oxygen species and nitrogen species, release lytic enzymes, and ingest microbes. In addition, they secrete chemokines that then attract more inflammatory cells. Finally, activated neutrophils undergo apoptosis, a process that plays a central role in the resolution of acute inflammation. A crucial event in successful resolution of acute inflammation is the release of endogenous antiinflammatory mediators and the replacement of apoptotic neutrophils by mononuclear cells. Monocytes then differentiate into macrophages that recognize and phagocytose apoptotic cells. Delayed apoptosis is associated with the prolongation and persistence of inflammatory disorders, including inflammatory bowel disease (11), acute respiratory distress syndrome (91), rheumatoid arthritis (70), chronic granulomatous disease (12), severe sepsis (46), and systemic inflammatory response syndrome (41).

Little is known about the signals that shut down acute inflammation or shift the inflammatory response from an acute

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into a chronic state. The aim of this review is to summarize the possible contribution of oxidized phospholipids, which are generated during inflammation-induced apoptosis, to the processes of resolution of acute and the propagation of chronic inflammatory reactions.

FORMATION OF OXIDIZED PHOSPHOLIPIDS DURING APOPTOSIS

Phospholipid oxidation products serve as recognition signals on apoptotic cells

During inflammatory processes, reactive oxygen species are released by activated neutrophils that not only kill invading microorganisms, but also modify host molecules such as lipids, proteins, and DNA. Thus, to prevent uncontrolled inflammatory responses and persistent inflammation, activated neutrophils undergo apoptosis leading to formation of recognition signals on the cell membrane, resulting in prompt phagocytosis of apoptotic cells by macrophages. The loss of the plasma membrane phospholipid asymmetry leading to externalization of phosphatidylserine (PS) to the outer leaflet of the membrane is an important signal for macrophage recognition of aged and apoptotic cells (1, 9, 43, 75). It has been shown that activation of the NADPH oxidase during apoptosis leads to predominant oxidation of the membrane PS, but also phosphatidylcholine (PC) and phosphatidylethanolamine (PE). Using the pancaspase inhibitor, z-VAD-fmk, it has been shown that apoptosis-associated oxidation of PS could be prevented in dimethyl sulfoxide-differentiated HL-60 cells, whereas PC and PE were oxidized to the same extent in the absence or presence of z-VAD-fmk (5). In apoptotic cells, both unoxidized PS and oxidized PS are externalized and serve as distinct signals for phagocytosis by macrophages. Oxidation of PS has been shown after induction of apoptosis in dimethyl sulfoxide-differentiated HL-60 cells, human blood neutrophils (5, 57), Jurkat cells (44), and normal human epidermal keratinocytes (80).

The importance of the externalized oxidized and unoxidized PS for phagocytosis of apoptotic cells and successful resolution of inflammation has been evaluated by competition studies using PS-containing liposomes, which could inhibit the uptake of apoptotic cells by macrophages *in vitro* (44). Moreover, by using such liposomes in a pulmonary inflammation model in the mouse, clearance of apoptotic cells in the bronchoalveolar fluid was inhibited, leading to massive accumulation of apoptotic cells and secondary necrosis (58). Thus, it could be suggested that whenever massive apoptosis and membrane blebbing occur, these formed blebs compete with apoptotic cells for phagocytosis and inhibit their clearance, resulting in a shift from apoptotic to necrotic cell death. In contrast to apoptosis, during necrosis, membrane integrity is lost and oxidants and histotoxic substances are massively released into the extracellular space, leading to severe tissue damage and delayed resolution of inflammation.

The presence of oxidized PC on the surface of apoptotic cells has been demonstrated by using the monoclonal antibody EO6 that recognizes oxidized low-density lipoprotein (LDL). This antibody exclusively binds to oxidized PC (13, 36). It has been shown that EO6 can effectively block the uptake of apoptotic cells by macrophages (13). Thus, in addition to oxidized PS, the presence of oxidatively modified PC is an important signal for phagocytosis.

Receptors involved in the recognition of oxidized phospholipids on apoptotic cells

Various receptors have been implicated to participate in the recognition of apoptotic cells by phagocytes (for review, see 76). Some of these receptors were identified as recognizing oxidized epitopes on apoptotic cells. Among these, CD14 (21, 59), CD36 (25), CD68 (75), the class B scavenger receptors type I (27), the scavenger receptor class A (72), and the lectin-like oxidized LDL receptor 1 (67) have been reported to bind apoptotic cells; interestingly, all of them were originally identified as receptors for oxidatively modified LDL, suggesting an oxidized lipid moiety on the apoptotic cell as the ligand (69, 75, 83). Recently, by using nonapoptotic Jurkat cells whose plasma membranes had been enriched with oxidized PS, it was shown that antibodies against CD36 and against the phosphatidylserine receptor inhibited the uptake of these cells by macrophages. Thus, it has been suggested that CD36 and the PS receptor recognize oxidized PS (45).

Besides the above-mentioned receptors, Chang *et al.* showed that C-reactive protein (CRP) binds to oxidized LDL, oxidized PC, and also apoptotic cells (14). The CRP-oxidized phospholipid complexes can then be taken up by macrophages via the "CRP receptor" (CD32 or $F_c\gamma$-II receptor) or other scavenger receptors such as CD36 (34).

Membrane vesicles and apoptotic blebs contain biologically active oxidized phospholipids

Besides the loss of the plasma membrane phospholipid asymmetry, apoptotic cells undergo a typical morphological transformation by the release of membrane blebs (apoptotic blebs) (15, 60). In addition to apoptosis, membrane vesiculation occurs in various cell types upon stimulation with Ca^{2+} ionophore, lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), thrombin, complement proteins C5b-9, or hydroperoxides (16, 26, 33, 62, 71, 98; for review, see 86).

Recently, Huber *et al.* from our laboratory showed that apoptotic endothelial blebs stimulated endothelial cells to bind monocytes, but not neutrophils, whereas membrane vesicles from activated endothelial cells failed to induce monocyte binding (37). However, *in vitro* oxidation of membrane vesicles from activated endothelial cells rendered them biologically active by generation of 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphorylcholine (POVPC) (37). Moreover, we showed that the ability of apoptotic blebs or oxidized vesicles to induce monocyte adhesion was abolished by preincubation with antibodies against oxidized PC (EO6). On the other hand, an antibody that recognizes malondialdehyde-lysine epitopes (EO14) failed to inhibit the activity of apoptotic blebs, confirming oxidized phospholipids as the biologically active compounds in apoptotic blebs and oxidized membrane vesicles (37).

Various diseases have been shown to be accompanied by elevated levels of circulating microvesicles and apoptotic blebs from various cell types. Most of these diseases were also accompanied by elevated thrombotic risk, such as atherosclero-

sis (54), myocardial infarction (10), transient ischemic attacks, lacunar infarction and multiinfarct dementia (28, 49), acute coronary syndrome (55), disorders characterized by the presence of lupus anticoagulant (16), uremia (4), diabetes (22, 68), thrombotic thrombocytopenic purpura (40), heparin-induced thrombocytopenia (88), meningococcal sepsis (66), but also in multiple sclerosis (61) and after clinical interventions such as cardiac surgery (1), plasmapheresis (96), and after cardiopulmonary bypass (65). Moreover, it has been described that various tumor cell lines and tumors continually shed membrane vesicles *in vitro* and *in vivo* (24, 31). In spite of the vast amount of data documenting the presence of membrane blebs *in vivo,* their role in activating cells and inducing transcription of pro- and antiinflammatory genes has been less appreciated.

PROPAGATION OF CHRONIC INFLAMMATION BY OXIDIZED PHOSPHOLIPIDS

Oxidized phospholipids induce monocyte–endothelial interactions

Accumulation of monocytic cells is a hallmark of chronic inflammation. Lipid oxidation products are believed to play crucial roles in propagating the chronic inflammatory processes underlying the development of atherosclerotic lesions (52). Entrapment and oxidation of LDLs in the subendothelial space are key events in the development of atherosclerosis (6, 64). Minimally modified/oxidized LDL (MM-LDL) is capable of inducing an inflammatory response in endothelial cells by production of chemokines such as monocyte chemoattractant protein-1 (MCP-1) (17) and Gro-1 (77), which promote recruitment of monocytes to the subintimal space, where they differentiate into macrophages. Oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine(OxPAPC) and three of its components, POVPC, 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine (PGPC), and 1-palmitoyl-2-(5,6-epoxyisoprostane E_2)-*sn*-glycero-3-phosphocholine(PEIPC), were shown to be active components of MM-LDL (90). It was shown that MM-LDL and POVPC induce specific monocyte adhesion by a mechanism involving endothelial surface expression of an alternatively spliced form of fibronectin, connecting segment-1, a counterligand for VLA-4 on monocytes (79).

Induction of signaling mechanisms and gene expression by oxidized phospholipids

Oxidized phospholipids induce a specific set of proinflammatory genes *in vitro* and *in vivo.* Besides MCP-1, Gro-1, and interleukin (IL)-8 (17, 74, 77, 82), recently also other chemokines such as macrophage inflammatory protein-1α (MIP-1α), MIP-1β, RANTES, MIP-2, and interferon-inducible protein-10 have been shown to be up-regulated by oxidized phospholipids (81 and unpublished observation). Moreover, we could show that oxidized phospholipids increase synthesis of the transcription factor early growth response 1 (EGR-1) in endothelial cells and so induce expression of tissue factor (8). Various signaling mechanisms are activated by oxidized phospholipids in endothelial cells. These include elevation of cyclic AMP and cytosolic Ca^{2+} levels and activation of mitogen-activated protein (MAP) kinase cascades by protein kinases A and C, but also induction of MAP kinase phosphatase 1. Activation of transcription is mediated by Egr-1 and NFAT (nuclear factor of activated T cells), cyclic AMP responsive element binding protein, and peroxisome proliferator-activated receptors (and PPARs). However, we clearly demonstrated that oxidized phospholipids do not engage the classical inflammatory nuclear factor-κB pathway (8).

POSSIBLE ROLE OF OXIDIZED PHOSPHOLIPIDS IN THE RESOLUTION OF ACUTE INFLAMMATION

Heme oxygenase-1 (HO-1) and cyclooxygenase-2 (COX-2) play important roles in the resolution of inflammation

A self-limiting acute infection is characterized by rapid edema formation, massive recruitment of PMNs and their subsequent apoptosis, followed by attraction of mononuclear cells that phagocytose apoptotic cells and injurious stimuli. Finally, normal tissue function and structure are restored [as reviewed by Lawrence *et al.* (47)]. Whenever this procedure becomes dysregulated, chronic inflammation can occur. Hence, the mechanisms involved in the endogenous antiinflammatory and inflammation-resolving process are currently extensively investigated, as they could offer possible targets in the treatment of chronic inflammation.

Using the carrageenin pleurisy model, one of the most widely characterized acute inflammatory models, Willoughby *et al.* (95) showed that two enzymes, COX-2 and HO-1, are essential for the resolving phase because the inhibition of these enzymes delayed the resolution of inflammation. Although COX-2 was initially described as a proinflammatory gene because of the beneficial effects of pharmacological COX-2 inhibitors, antiinflammatory properties also have been ascribed to COX-2 (for review, see 29). It has been shown that COX-2 expression was biphasic, the first peak occurring within the first 2 h and the second, much higher peak occurring after 48 h. It was shown that this late expression of COX-2 was essential for resolving the inflammation, because inhibition of this second peak resulted in a delayed inflammatory reaction (30). HO-1, the inducible rate-limiting enzyme mediating catabolism of heme into biliverdin, free iron, and carbon monoxide (53), was shown to be highly induced in the carrageenin pleurisy model 24 h after induction of inflammation. Inhibition of HO-1 resulted in increased cell extravasation (93). Elevation of HO-1 resulted in suppression of the inflammatory process, whereas inhibition of HO-1 led to a prolongation and potentiation of inflammation (94).

Genes induced by oxidized phospholipids that are involved in the resolution of inflammation

Taking into consideration that apoptosis is essential for a complete resolution of acute inflammation and the fact that oxidized phospholipids are generated during apoptosis, we hypothesize that oxidized phospholipids contribute to the res-

olution of inflammation at several levels of the resolution process:

First, PMNs have to be replaced and phagocytosed by macrophages, which in turn have to be attracted by specific chemokines. Oxidized phospholipids are capable of inducing MCP-1, IL-8, and Gro-1 and also induce specific binding of monocytes, but not neutrophils to endothelial cells *in vitro* (17, 74, 77, 82). Although the contribution of oxidized phospholipids to the selective accumulation of mononuclear cells in atherosclerotic plaques was suggested (52), until now they were not implicated in the replacement of PMNs during cessation of acute inflammation. Second, oxidized phospholipids were also shown to induce the expression of enzymes, important for a sufficient resolution of acute inflammation, such as HO-1 (38) and COX-2 (73). The importance of these enzymes in resolution of acute inflammation has been described above. Third, oxidized LDL was shown to induce the antiinflammatory IL-10 (87), which inhibits activation and function of macrophages by suppressing phagocytosis, oxidative burst, and production of nitric oxide and cytokines (32). Moreover, IL-10 counteracts cytokine-induced inhibition of neutrophil apoptosis during severe sepsis (46). Oxidized phospholipids were also shown to induce IL-6 (85). Although several lines of evidence suggest that IL-6 has crucial roles in the early phase of inflammation (3), the essential involvement of IL-6 in wound healing has been recently demonstrated (51). In addition, oxidized phospholipids were demonstrated to induce glutathione synthesis (63), which protects cells against oxidative stress (23). Lately, it has been proposed that oxidized phospholipids can also act as ligands and agonists of the PPAR γ (18, 73, 81, 84) and PPARα (19, 48). The antiinflammatory properties of PPARs are increasingly recognized (35) and have been reviewed elsewhere (20). In particular, it has been described that PPARα activation leads to induction of IκBα expression (19), and that PPARγ activation suppresses LPS, TNF-α, or interferon-γ-induced inflammatory responses (39, 56, 92).

Oxidized phospholipids present in membrane vesicles are biologically active in vivo

Although it is believed that lipid oxidation products can exert their biological activities locally, *e.g.,* in the vessel wall where they accumulate, it was not clear whether they are active also in the bloodstream. Several plasma enzymes, including paraoxonase (2, 78), platelet activating factor-acetylhydrolase (89, 97), or secretory nonpancreatic phospholipase A_2 (50), have been shown to destroy biologically active phospholipids. However, we showed that intravenously administered OxPAPC exerted dose-dependent gene induction of *egr-1* in the liver of mice. Moreover, JE (the mouse homologue of MCP-1) and HO-1 were up-regulated in various tissues, including liver, heart, and white blood cells (42), upon intravenous administration of OxPAPC.

We examined whether oxidized membrane vesicles, which were shown to have similar properties as apoptotic blebs and OxPAPC *in vitro* (37), would exert similar biological effects also *in vivo*. Isolated membrane vesicles from activated endothelial cells were oxidized and injected intravenously into mice. Oxidized membrane vesicles induced HO-1 expression in the liver after 4.5 h, whereas E-selectin, a marker of acute inflammation, was not up-regulated (Fig. 1). Thus, we conclude that lipid oxidation products present in membrane vesicles and apoptotic cells are biologically active and can induce gene expression *in vivo*.

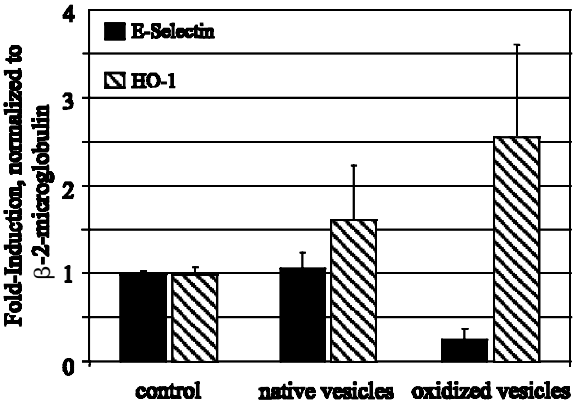

FIG. 1. Oxidized membrane vesicles induce HO-1 expression in the liver of mice. Microvesicles were derived from endothelial cells exposed for 45 min to Ca^{2+} ionophore (10 µmol/L) in modified Hanks' balanced salt solution containing 2.5 mmol/L $CaCl_2$ and 10 mmol/L HEPES (37). Oxidation was induced by *tert*-butyl hydroperoxide (30 µmol/L) and Fe^{2+} (5 µmol/L) for 75 min at 37°C. Thirty micrograms of native or oxidized vesicles was injected intravenously into female C57/BL6 mice (n = 3). After 4.5 h, animals were killed and RNA was isolated from the liver using Trizol reagent; 900 ng of total RNA was reverse-transcribed. Quantitative RT-PCR for HO-1 and E-selectin was performed using cDNA corresponding to 2.5 ng of total RNA. Gene expression was normalized to β-2-microglobulin. Results are shown as means ± SE (42).

ANTIENDOTOXIN EFFECT OF OXIDIZED PHOSPHOLIPIDS

In addition to the induction of antiinflammatory and protective genes, we recently found that OxPAPC inhibits LPS-induced inflammatory reactions by interacting with accessory plasma proteins CD14 and LPS-binding protein (LBP), which present LPS to its receptor, toll-like receptor 4 (TLR4). The effect was specific for LPS; OxPAPC did not significantly influence actions of other proinflammatory agents, such as IL-1β or TNF-α. We could also show in several *in vivo* models that OxPAPC inhibited typical signs of inflammation, such as leukocyte accumulation, edema formation, and expression of adhesion molecules such as E-selectin, in mice challenged with LPS. Furthermore, survival of animals receiving a lethal dose of LPS was significantly increased by OxPAPC (7). This mechanism of scavenging accessory proteins by OxPAPC, thereby inhibiting LPS signaling, may represent a negative feedback during gram-negative inflammation to blunt innate immune responses. As it was shown that during apoptosis membrane phospholipids, particularly PS, are oxidized, we were interested whether oxidized PS, in addition to oxidized PC, also had the ability to block LPS-induced inflammatory reactions. As illustrated in Fig. 2, LPS-induced E-selectin expression on endothelial cells was inhibited by oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphatidylserine (OxPAPS), suggesting

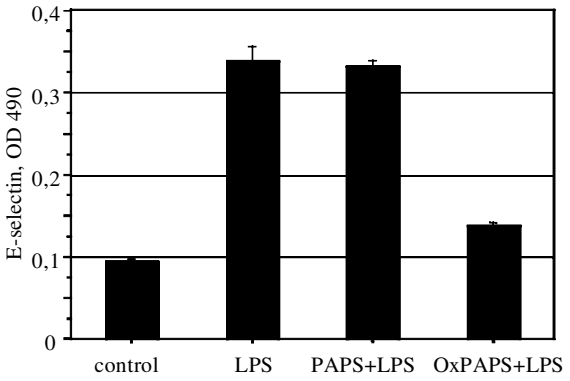

FIG. 2. OxPAPS inhibits LPS-induced E-selectin expression. Monolayers of human umbilical vein endothelial cells were stimulated with 300 ng/ml LPS alone or in combination with 5 μg of PAPS or OxPAPS in Medium 199 containing 10% fetal calf serum for 4 h. The ELISA was performed as described previously (7) using E-selectin antibody (R&D Systems), secondary peroxidases-conjugated antibody, and *o*-phenylenediamine as substrate. Results are shown as means ± SD.

that oxidized PS that is formed during apoptosis exerts anti-endotoxin effects.

Based on these findings, we hypothesize that oxidized phospholipids that emerge during apoptosis positively regulate the resolution of acute bacterial inflammation, on the one hand by inducing protective, antiinflammatory genes, and on the other hand by representing a negative feedback by inhibiting LPS action and thus blunting innate immune response.

CONCLUSION

At sites of inflammation, apoptosis with subsequent exposure of oxidized phospholipids (especially PS) occurs, oxidized membrane vesicles and apoptotic blebs are released from various cell types, and reactive oxygen species are released into the extracellular space that render other plasma membranes as well as membrane vesicles biologically active. We hypothesize that these newly formed, accumulating oxidized phospholipids contribute to the process of resolution of inflammation by (1) inducing selective monocyte recruitment via induction of the chemokines MCP-1, IL-8, and Gro-1, (2) representing recognition signals of apoptotic cells for macrophages for phagocytosis, (3) inducing enzymes that are essential for resolution such as COX-2 and HO-1 and suppressing oxidative burst via IL-10, and (4) repressing LPS-induced inflammation (Fig. 3).

On the other hand, under circumstances of ongoing increased oxidative stress, *e.g.,* when apoptosis of neutrophils is delayed,

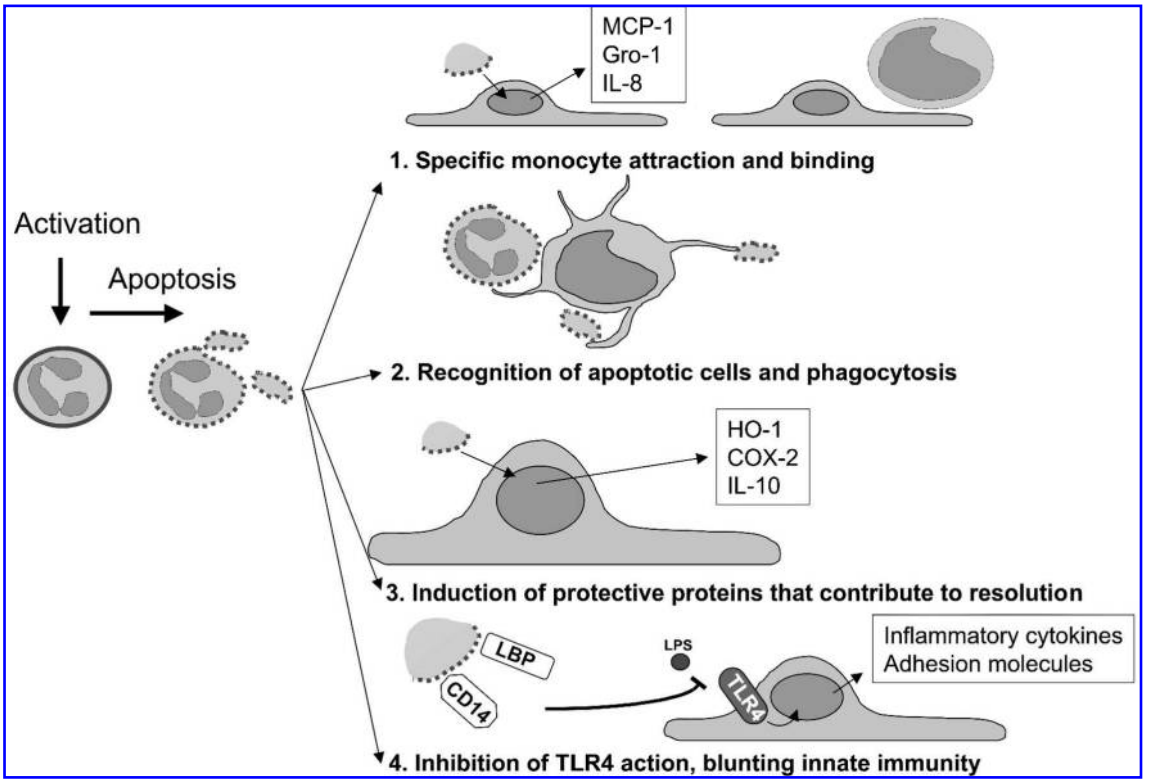

FIG 3. Activated neutrophils at the site of inflammation undergo rapid apoptosis, leading to loss of plasma asymmetry, and thus to oxidation and externalization of phosphatidylserine (.....), and membrane shedding. (**1**) Oxidized membranes stimulate endothelial cells to produce MCP-1, Gro-1, and IL-8; thus, monocytes are specifically attracted. (**2**) Exposure of the oxidized phosphatidylserine on the outer leaflet of the membrane is rapidly recognized by macrophages, leading to phagocytosis. (**3**) Oxidized membranes can contribute to cell protection and resolution of inflammation by induction of HO-1, COX-2, and IL-10 (see text). (**4**) Oxidized membranes can interact with CD14 and LBP and thereby inhibit LPS-induced inflammatory response by inhibiting signaling through Toll-like receptor 4.

the presence of these lipid mediators would be prolonged, leading to ongoing accumulation of mononuclear cells at the site of inflammation and a pathology typical for chronic inflammation. Besides atherosclerosis, the classical "lipid-induced" inflammation, there are many other chronic inflammatory diseases accompanied by massive oxidative stress and apoptosis such as rheumatoid arthritis, asthma, preeclampsia, or cancer-related inflammation, in which oxidized phospholipids may play an important role in modulating the disease progress.

However, more work has to be done to understand how oxidized phospholipids can promote the resolution of inflammation and under which circumstances they act as proinflammatory agents leading to prolonged, chronic inflammation.

ABBREVATIONS

COX-2, cyclooxygenase-2; CRP, C-reactive protein; EGR-1, early growth response 1; HO-1, heme oxygenase-1; IL, interleukin; LBP, lipopolysaccharide-binding protein; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MAP, mitogen-activated protein; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inflammatory protein-1; MM-LDL, minimally modified low-density lipoprotein; OxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; OxPAPS, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphatidylserine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PMNs, polymorphonuclear leukocytes; POVPC, 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphorylcholine; PPAR, peroxisome proliferator-activated receptor; PS, phosphatidylserine; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α.

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