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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 atheroscle-

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

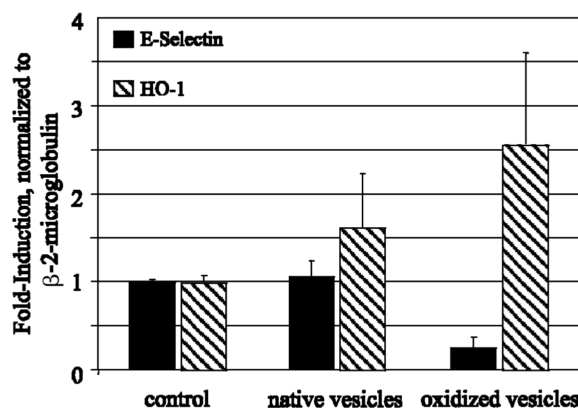

FIG. 1. Oxidized membrane vesicles induce HO-1 expression in the liver of mice. Microvesicles were derived from endothelial cells exposed for 45 min to Ca^{2+} ionophore (10 µmol/L) in modified Hanks' balanced salt solution containing 2.5 mmol/L $CaCl_2$ and 10 mmol/L HEPES (37). Oxidation was induced 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).

lipid oxidation products present in membrane vesicles and apoptotic cells are biologically active and can induce gene expression *in vivo.*

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

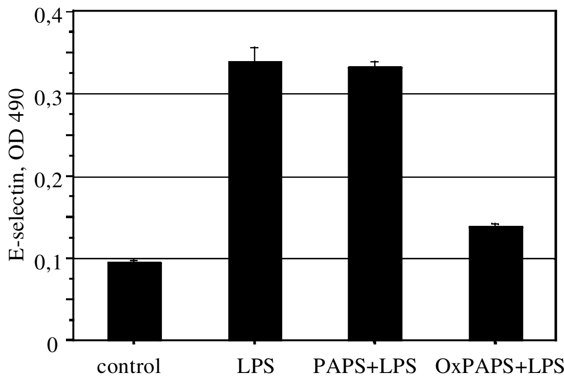

FIG. 2. OxPAPS inhibits LPS-induced E-selectin expression. Monolayers of human umbilical vein endothelial cells were stimulated with 300 ng/ml LPS alone or in combination with 5 μg of PAPS or OxPAPS in Medium 199 containing 10% fetal calf serum for 4 h. The ELISA was performed as described previously (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 antiendotoxin 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,

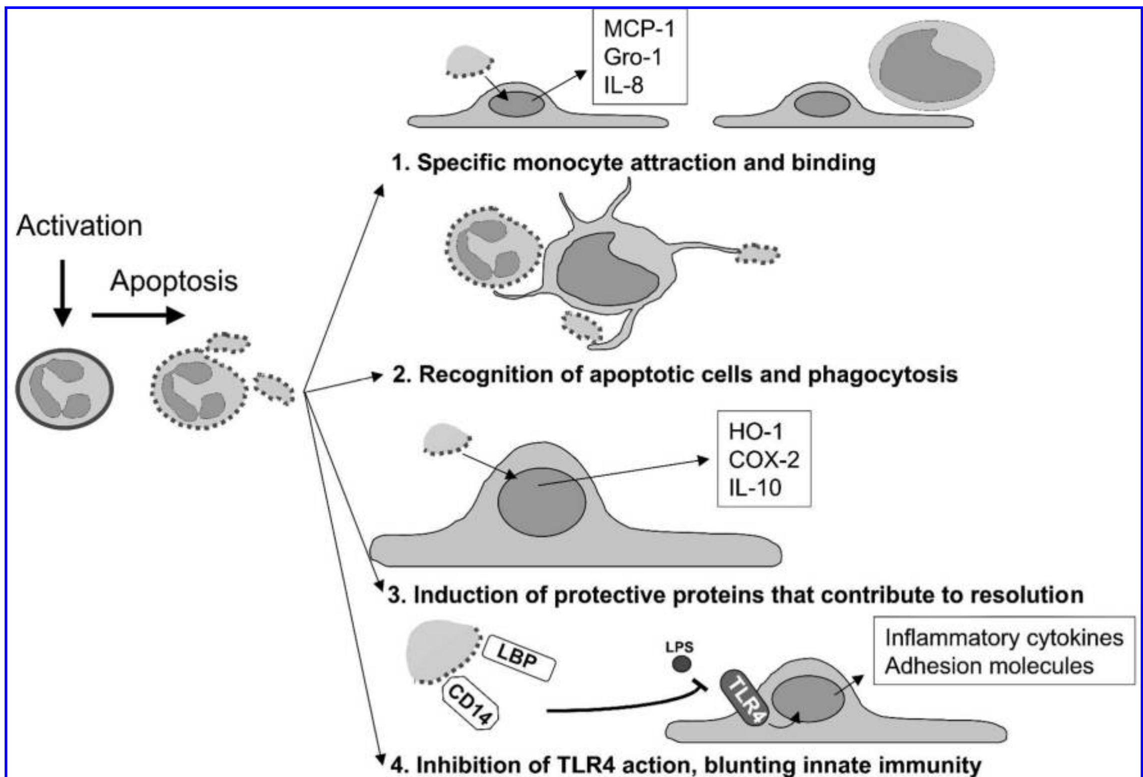

FIG 3. Activated neutrophils at the site of inflammation undergo rapid apoptosis, leading to loss of plasma asymmetry, and thus to oxidation and externalization of phosphatidylserine ( ), and membrane shedding. (**1**) Oxidized membranes stimulate endothelial cells to produce MCP-1, Gro-1, and IL-8; 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.

REFERENCES

1. Abrams CS, Ellison N, Budzynski AZ, and Shattil SJ. Direct detection of activated platelets and platelet-derived microparticles in humans. *Blood* 75: 128–138, 1990.
2. Ahmed Z, Ravandi A, Maguire GF, Emili A, Draganov D, La Du BN, Kuksis A, and Connelly PW. Multiple substrates for paraoxonase-1 during oxidation of phosphatidylcholine by peroxynitrite. *Biochem Biophys Res Commun* 290: 391–396, 2002.
3. Akira S and Kishimoto T. IL-6 and NF-IL6 in acute-phase response and viral infection. *Immunol Rev* 127: 25–50, 1992.
4. Ando M, Iwata A, Ozeki Y, Tsuchiya K, Akiba T, and Nihei H. Circulating platelet-derived microparticles with procoagulant activity may be a potential cause of thrombosis in uremic patients. *Kidney Int* 62: 1757–1763, 2002.
5. Arroyo A, Modriansky M, Serinkan FB, Bello RI, Matsura T, Jiang J, Tyurin VA, Tyurina YY, Fadeel B, and Kagan VE. NADPH oxidase-dependent oxidation and externalization of phosphatidylserine during apoptosis in Me2SO-differentiated HL-60 cells. Role in phagocytic clearance. *J Biol Chem* 277: 49965–49975, 2002.
6. Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, and Lusis AJ. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation* 91: 2488–2496, 1995.
7. Bochkov VN, Kadl A, Huber J, Gruber F, Binder BR, and Leitinger N. Protective role of phospholipid oxidation products in endotoxin-induced tissue damage. *Nature* 419: 77–81, 2002.
8. Bochkov VN, Mechtcheriakova D, Lucerna M, Huber J, Malli R, Graier WF, Hofer E, Binder BR, and Leitinger N. Oxidized phospholipids stimulate tissue factor expression in human endothelial cells via activation of ERK/EGR-1 and Ca^{++}/NFAT. *Blood* 99: 199–206, 2002.
9. Borisenko GG, Matsura T, Liu SX, Tyurin VA, Jianfei J, Serinkan FB, and Kagan VE. Macrophage recognition of externalized phosphatidylserine and phagocytosis of apoptotic Jurkat cells—existence of a threshold. *Arch Biochem Biophys* 413: 41–52, 2003.
10. Boulanger CM, Scoazec A, Ebrahimian T, Henry P, Mathieu E, Tedgui A, and Mallat Z. Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. *Circulation* 104: 2649–2652, 2001.
11. Brannigan AE, O'Connell PR, Hurley H, O'Neill A, Brady HR, Fitzpatrick JM, and Watson RW. Neutrophil apoptosis is delayed in patients with inflammatory bowel disease. *Shock* 13: 361–366, 2000.
12. Brown JR, Goldblatt D, Buddle J, Morton L, and Thrasher AJ. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease (CGD). *J Leukoc Biol* 73: 591–599, 2003.
13. Chang MK, Bergmark C, Laurila A, Horkko S, Han KH, Friedman P, Dennis EA, and Witztum JL. Monoclonal antibodies against oxidized low-density lipoprotein bind to apoptotic cells and inhibit their phagocytosis by elicited macrophages: evidence that oxidation-specific epitopes mediate macrophage recognition. *Proc Natl Acad Sci U S A* 96: 6353–6358, 1999.
14. Chang MK, Binder CJ, Torzewski M, and Witztum JL. C-reactive protein binds to both oxidized LDL and apoptotic cells through recognition of a common ligand: phosphorylcholine of oxidized phospholipids. *Proc Natl Acad Sci U S A* 99: 13043–13048, 2002.
15. Coleman ML, Sahai EA, Yeo M, Bosch M, Dewar A, and Olson MF. Membrane blebbing during apoptosis results from caspase-mediated activation of ROCK I. *Nat Cell Biol* 3: 339–345, 2001.
16. Combes V, Simon AC, Grau GE, Arnoux D, Camoin L, Sabatier F, Mutin M, Sanmarco M, Sampol J, and Dignat-George F. In vitro generation of endothelial microparticles and possible prothrombotic activity in patients with lupus anticoagulant. *J Clin Invest* 104: 93–102, 1999.
17. Cushing SD, Berliner JA, Valente AJ, Territo MC, Navab M, Parhami F, Gerrity R, Schwartz CJ, and Fogelman AM. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc Natl Acad Sci U S A* 87: 5134–5138, 1990.
18. Davies SS, Pontsler AV, Marathe GK, Harrison KA, Murphy RC, Hinshaw JC, Prestwich GD, Hilaire AS, Prescott SM, Zimmerman GA, and McIntyre TM. Oxidized alkyl phospholipids are specific, high affinity peroxisome proliferator-activated receptor gamma ligands and agonists. *J Biol Chem* 276: 16015–16023, 2001.

19. Delerive P, Furman C, Teissier E, Fruchart J, Duriez P, and Staels B. Oxidized phospholipids activate PPARalpha in a phospholipase A2-dependent manner. *FEBS Lett* 471: 34–38, 2000.
20. Delerive P, Fruchart JC, and Staels B. Peroxisome proliferator-activated receptors in inflammation control. *J Endocrinol* 169: 453–459, 2001.
21. Devitt A, Moffatt OD, Raykundalia C, Capra JD, Simmons DL, and Gregory CD. Human CD14 mediates recognition and phagocytosis of apoptotic cells. *Nature* 392: 505–509, 1998.
22. Diamant M, Nieuwland R, Pablo RF, Sturk A, Smit JW, and Radder JK. Elevated numbers of tissue-factor exposing microparticles correlate with components of the metabolic syndrome in uncomplicated type 2 diabetes mellitus. *Circulation* 106: 2442–2447, 2002.
23. Dickinson DA, Moellering DR, Iles KE, Patel RP, Levonen AL, Wigley A, Darley-Usmar VM, and Forman HJ. Cytoprotection against oxidative stress and the regulation of glutathione synthesis. *Biol Chem* 384: 527–537, 2003.
24. Dolo V, Ginestra A, Cassara D, Violini S, Lucania G, Torrisi MR, Nagase H, Canevari S, Pavan A, and Vittorelli ML. Selective localization of matrix metalloproteinase 9, beta1 integrins, and human lymphocyte antigen class I molecules on membrane vesicles shed by 8701-BC breast carcinoma cells. *Cancer Res* 58: 4468–4474, 1998.
25. Fadok VA, Warner ML, Bratton DL, and Henson PM. CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (alpha v beta 3). *J Immunol* 161: 6250–6257, 1998.
26. Fourcade O, Simon MF, Viode C, Rugani N, Leballe F, Ragab A, Fournie B, Sarda L, and Chap H. Secretory phospholipase A2 generates the novel lipid mediator lysophosphatidic acid in membrane microvesicles shed from activated cells. *Cell* 80: 919–927, 1995.
27. Fukasawa M, Adachi H, Hirota K, Tsujimoto M, Arai H, and Inoue K. SRB1, a class B scavenger receptor, recognizes both negatively charged liposomes and apoptotic cells. *Exp Cell Res* 222: 246–250, 1996.
28. Geiser T, Sturzenegger M, Genewein U, Haeberli A, and Beer JH. Mechanisms of cerebrovascular events as assessed by procoagulant activity, cerebral microemboli, and platelet microparticles in patients with prosthetic heart valves. *Stroke* 29: 1770–1777, 1998.
29. Gilroy DW and Colville-Nash PR. New insights into the role of COX 2 in inflammation. *J Mol Med* 78: 121–129, 2000.
30. Gilroy DW, Colville-Nash PR, Willis D, Chivers J, Paul-Clark MJ, and Willoughby DA. Inducible cyclooxygenase may have anti-inflammatory properties. *Nat Med* 5: 698–701, 1999.
31. Ginestra A, La Placa MD, Saladino F, Cassara D, Nagase H, and Vittorelli ML. The amount and proteolytic content of vesicles shed by human cancer cell lines correlates with their in vitro invasiveness. *Anticancer Res* 18: 3433–3437, 1998.
32. Haddad JJ and Fahlman CS. Redox- and oxidant-mediated regulation of interleukin-10: an anti-inflammatory, antioxidant cytokine? *Biochem Biophys Res Commun* 297: 163–176, 2002.
33. Hamilton KK, Hattori R, Esmon CT, and Sims PJ. Complement proteins C5b-9 induce vesiculation of the endothelial plasma membrane and expose catalytic surface for assembly of the prothrombinase enzyme complex. *J Biol Chem* 265: 3809–3814, 1990.
34. Hazen SL and Chisolm GM. Oxidized phosphatidylcholines: pattern recognition ligands for multiple pathways of the innate immune response. *Proc Natl Acad Sci U S A* 99: 12515–12517, 2002.
35. Henson P. Suppression of macrophage inflammatory responses by PPARs. *Proc Natl Acad Sci U S A* 100: 6295–6296, 2003.
36. Horkko S, Bird DA, Miller E, Itabe H, Leitinger N, Subbanagounder G, Berliner JA, Friedman P, Dennis EA, Curtiss LK, Palinski W, and Witztum JL. Monoclonal autoantibodies specific for oxidized phospholipids or oxidized phospholipid–protein adducts inhibit macrophage uptake of oxidized low-density lipoproteins. *J Clin Invest* 103: 117–128, 1999.
37. Huber J, Vales A, Mitulovic G, Blumer M, Schmid R, Witztum JL, Binder BR, and Leitinger N. Oxidized membrane vesicles and blebs from apoptotic cells contain biologically active oxidized phospholipids that induce monocyte–endothelial interactions. *Arterioscler Thromb Vasc Biol* 22: 101–107, 2002.
38. Ishikawa K, Navab M, Leitinger N, Fogelman AM, and Lusis AJ. Induction of heme oxygenase-1 inhibits the monocyte transmigration induced by mildly oxidized LDL. *J Clin Invest* 100: 1209–1216, 1997.
39. Jiang C, Ting AT, and Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature* 391: 82–86, 1998.
40. Jimenez JJ, Jy W, Mauro LM, Horstman LL, and Ahn YS. Elevated endothelial microparticles in thrombotic thrombocytopenic purpura: findings from brain and renal microvascular cell culture and patients with active disease. *Br J Haematol* 112: 81–90, 2001.
41. Jimenez MF, Watson RW, Parodo J, Evans D, Foster D, Steinberg M, Rotstein OD, and Marshall JC. Dysregulated expression of neutrophil apoptosis in the systemic inflammatory response syndrome. *Arch Surg* 132: 1263–1269, 1997.
42. Kadl A, Huber J, Gruber F, Bochkov VN, Binder BR, and Leitinger N. Analysis of inflammatory gene induction by oxidized phospholipids in vivo by quantitative real-time RT-PCR in comparison with effects of LPS. *Vascul Pharmacol* 38: 219–227, 2002.
43. Kagan VE, Fabisiak JP, Shvedova AA, Tyurina YY, Tyurin VA, Schor NF, and Kawai K. Oxidative signaling pathway for externalization of plasma membrane phosphatidylserine during apoptosis. *FEBS Lett* 477: 1–7, 2000.
44. Kagan VE, Gleiss B, Tyurina YY, Tyurin VA, Elenstrom-Magnusson C, Liu SX, Serinkan FB, Arroyo A, Chandra J, Orrenius S, and Fadeel B. A role for oxidative stress in apoptosis: oxidation and externalization of phosphatidylserine is required for macrophage clearance of cells undergoing Fas-mediated apoptosis. *J Immunol* 169: 487–499, 2002.
45. Kagan VE, Borisenko GG, Serinkan BF, Tyurina YY, Tyurin VA, Jiang J, Liu SX, Shvedova AA, Fabisiak JP,

Uthaisang W, and Fadeel B. Appetizing rancidity of apoptotic cells for macrophages: oxidation, externalization, and recognition of phosphatidylserine. *Am J Physiol Lung Cell Mol Physiol* 285: L1–L17, 2003.

46. Keel M, Ungethum U, Steckholzer U, Niederer E, Hartung T, Trentz O, and Ertel W. Interleukin-10 counterregulates proinflammatory cytokine-induced inhibition of neutrophil apoptosis during severe sepsis. *Blood* 90: 3356–3363, 1997.
47. Lawrence T, Willoughby DA, and Gilroy DW. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. *Nat Rev Immunol* 2: 787–795, 2002.
48. Lee H, Shi W, Tontonoz P, Wang S, Subbanagounder G, Hedrick CC, Hama S, Borromeo C, Evans RM, Berliner JA, and Nagy L. Role for peroxisome proliferator-activated receptor alpha in oxidized phospholipid-induced synthesis of monocyte chemotactic protein-1 and interleukin-8 by endothelial cells. *Circ Res* 87: 516–521, 2000.
49. Lee YJ, Jy W, Horstman LL, Janania J, Reyes Y, Kelley RE, and Ahn YS. Elevated platelet microparticles in transient ischemic attacks, lacunar infarcts, and multiinfarct dementias. *Thromb Res* 72: 295–304, 1993.
50. Leitinger N, Watson AD, Hama SY, Ivandic B, Qiao JH, Huber J, Faull KF, Grass DS, Navab M, Fogelman AM, de Beer FC, Lusis AJ, and Berliner JA. Role of group II secretory phospholipase A2 in atherosclerosis. 2. Potential involvement of biologically active oxidized phospholipids. *Arterioscler Thromb Vasc Biol* 19: 1291–1298, 1999.
51. Lin ZQ, Kondo T, Ishida Y, Takayasu T, and Mukaida N. Essential involvement of IL-6 in the skin wound-healing process as evidenced by delayed wound healing in IL-6-deficient mice. *J Leukoc Biol* 73: 713–721, 2003.
52. Lusis AJ. Atherosclerosis. *Nature* 407: 233–241, 2000.
53. Maines MD. Heme oxygenase: function, multiplicity, regulatory mechanisms, and clinical applications. *FASEB J* 2: 2557–2568, 1988.
54. Mallat Z, Hugel B, Ohan J, Leseche G, Freyssinet JM, and Tedgui A. Shed membrane microparticles with procoagulant potential in human atherosclerotic plaques: a role for apoptosis in plaque thrombogenicity. *Circulation* 99: 348–353, 1999.
55. Mallat Z, Benamer H, Hugel B, Benessiano J, Steg PG, Freyssinet JM, and Tedgui A. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. *Circulation* 101: 841–843, 2000.
56. Marx N, Mach F, Sauty A, Leung JH, Sarafi MN, Ransohoff RM, Libby P, Plutzky J, and Luster AD. Peroxisome proliferator-activated receptor-gamma activators inhibit IFN-gamma-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells. *J Immunol* 164: 6503–6508, 2000.
57. Matsura T, Serinkan BF, Jiang J, and Kagan VE. Phosphatidylserine peroxidation/externalization during staurosporine-induced apoptosis in HL-60 cells. *FEBS Lett* 524: 25–30, 2002.
58. Medan D, Wang L, Yang X, Dokka S, Castranova V, and Rojanasakul Y. Induction of neutrophil apoptosis and secondary necrosis during endotoxin-induced pulmonary inflammation in mice. *J Cell Physiol* 191: 320–326, 2002.
59. Miller YI, Viriyakosol S, Binder CJ, Feramisco JR, Kirkland TN, and Witztum JL. Minimally modified LDL binds to CD14, induces macrophage spreading via TLR4/MD-2, and inhibits phagocytosis of apoptotic cells. *J Biol Chem* 278: 1561–1568, 2003.
60. Mills JC, Stone NL, Erhardt J, and Pittman RN. Apoptotic membrane blebbing is regulated by myosin light chain phosphorylation. *J Cell Biol* 140: 627–636, 1998.
61. Minagar A, Jy W, Jimenez JJ, Sheremata WA, Mauro LM, Mao WW, Horstman LL, and Ahn YS. Elevated plasma endothelial microparticles in multiple sclerosis. *Neurology* 56: 1319–1324, 2001.
62. Miyoshi H, Umeshita K, Sakon M, Imajoh-Ohmi S, Fujitani K, Gotoh M, Oiki E, Kambayashi J, and Monden M. Calpain activation in plasma membrane bleb formation during *tert*-butyl hydroperoxide-induced rat hepatocyte injury. *Gastroenterology* 110: 1897–1904, 1996.
63. Moellering DR, Levonen AL, Go YM, Patel RP, Dickinson DA, Forman HJ, and Darley-Usmar VM. Induction of glutathione synthesis by oxidized low-density lipoprotein and 1-palmitoyl-2-arachidonyl phosphatidylcholine: protection against quinone-mediated oxidative stress. *Biochem J* 362: 51–59, 2002.
64. Navab M, Berliner JA, Watson AD, Hama SY, Territo MC, Lusis AJ, Shih DM, Van Lenten BJ, Frank JS, Demer LL, Edwards PA, and Fogelman AM. The Yin and Yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol* 16: 831–842, 1996.
65. Nieuwland R, Berckmans RJ, Rotteveel-Eijkman RC, Maquelin KN, Roozendaal KJ, Jansen PG, ten Have K, Eijsman L, Hack CE, and Sturk A. Cell-derived microparticles generated in patients during cardiopulmonary bypass are highly procoagulant. *Circulation* 96: 3534–3541, 1997.
66. Nieuwland R, Berckmans RJ, McGregor S, Boing AN, Romijn FP, Westendorp RG, Hack CE, and Sturk A. Cellular origin and procoagulant properties of microparticles in meningococcal sepsis. *Blood* 95: 930–935, 2000.
67. Oka K, Sawamura T, Kikuta K, Itokawa S, Kume N, Kita T, and Masaki T. Lectin-like oxidized low-density lipoprotein receptor 1 mediates phagocytosis of aged/apoptotic cells in endothelial cells. *Proc Natl Acad Sci U S A* 95: 9535–9540, 1998.
68. Omoto S, Nomura S, Shouzu A, Nishikawa M, Fukuhara S, and Iwasaka T. Detection of monocyte-derived microparticles in patients with Type II diabetes mellitus. *Diabetologia* 45: 550–555, 2002.
69. Ottnad E, Parthasarathy S, Sambrano GR, Ramprasad MP, Quehenberger O, Kondratenko N, Green S, and Steinberg D. A macrophage receptor for oxidized low density lipoprotein distinct from the receptor for acetyl low density lipoprotein: partial purification and role in recognition of oxidatively damaged cells. *Proc Natl Acad Sci U S A* 92: 1391–1395, 1995.
70. Ottonello L, Cutolo M, Frumento G, Arduino N, Bertolotto M, Mancini M, Sottofattori E, and Dallegri F. Synovial fluid from patients with rheumatoid arthritis inhibits neutrophil apoptosis: role of adenosine and proin-

flammatory cytokines. *Rheumatology (Oxford)* 41: 1249–1260, 2002.

71. Patel KD, Zimmerman GA, Prescott SM, and McIntyre TM. Novel leukocyte agonists are released by endothelial cells exposed to peroxide. *J Biol Chem* 267: 15168–15175, 1992.
72. Platt N, Suzuki H, Kurihara Y, Kodama T, and Gordon S. Role for the class A macrophage scavenger receptor in the phagocytosis of apoptotic thymocytes in vitro. *Proc Natl Acad Sci U S A* 93: 12456–12460, 1996.
73. Pontsler AV, St Hilaire A, Marathe GK, Zimmerman GA, and McIntyre TM. Cyclooxygenase-2 is induced in monocytes by peroxisome proliferator activated receptor gamma and oxidized alkyl phospholipids from oxidized low density lipoprotein. *J Biol Chem* 277: 13029–13036, 2002.
74. Reddy ST, Grijalva V, Ng C, Hassan K, Hama S, Mottahedeh R, Wadleigh DJ, Navab M, and Fogelman AM. Identification of genes induced by oxidized phospholipids in human aortic endothelial cells. *Vascul Pharmacol* 38: 211–218, 2002.
75. Sambrano GR and Steinberg D. Recognition of oxidatively damaged and apoptotic cells by an oxidized low density lipoprotein receptor on mouse peritoneal macrophages: role of membrane phosphatidylserine. *Proc Natl Acad Sci U S A* 92: 1396–1400, 1995.
76. Schlegel RA and Williamson P. Phosphatidylserine, a death knell. *Cell Death Differ* 8: 551–563, 2001.
77. Schwartz D, Andalibi A, Chaverri-Almada L, Berliner JA, Kirchgessner T, Fang ZT, Tekamp-Olson P, Lusis AJ, Gallegos C, Fogelman AM. Role of the GRO family of chemokines in monocyte adhesion to MM-LDL-stimulated endothelium. *J Clin Invest* 94: 1968–1973, 1994.
78. Shih DM, Gu L, Xia YR, Navab M, Li WF, Hama S, Castellani LW, Furlong CE, Costa LG, Fogelman AM, and Lusis AJ. Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. *Nature* 394: 284–287, 1998.
79. Shih PT, Elices MJ, Fang ZT, Ugarova TP, Strahl D, Territo MC, Frank JS, Kovach NL, Cabanas C, Berliner JA, and Vora DK. Minimally modified low-density lipoprotein induces monocyte adhesion to endothelial connecting segment-1 by activating beta1 integrin. *J Clin Invest* 103: 613–625, 1999.
80. Shvedova AA, Tyurina JY, Kawai K, Tyurin VA, Kommineni C, Castranova V, Fabisiak JP, and Kagan VE. Selective peroxidation and externalization of phosphatidylserine in normal human epidermal keratinocytes during oxidative stress induced by cumene hydroperoxide. *J Invest Dermatol* 118: 1008–1018, 2002.
81. Silva AR, de Assis EF, Caiado LF, Marathe GK, Bozza MT, McIntyre TM, Zimmerman GA, Prescott SM, Bozza PT, and Castro-Faria-Neto HC. Monocyte chemoattractant protein-1 and 5-lipoxygenase products recruit leukocytes in response to platelet-activating factor-like lipids in oxidized low-density lipoprotein. *J Immunol* 168: 4112–4120, 2002.
82. Subbanagounder G, Deng Y, Borromeo C, Dooley AN, Berliner JA, and Salomon RG. Hydroxy alkenal phospholipids regulate inflammatory functions of endothelial cells. *Vascul Pharmacol* 38: 201–209, 2002.
83. Terpstra V, Bird DA, and Steinberg D. Evidence that the lipid moiety of oxidized low density lipoprotein plays a role in its interaction with macrophage receptors. *Proc Natl Acad Sci U S A* 95: 1806–1811, 1998.
84. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, and Evans RM. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell* 93: 241–252, 1998.
85. Van Lenten BJ, Wagner AC, Navab M, and Fogelman AM. Oxidized phospholipids induce changes in hepatic paraoxonase and ApoJ but not monocyte chemoattractant protein-1 via interleukin-6. *J Biol Chem* 276: 1923–1929, 2001.
86. VanWijk MJ, VanBavel E, Sturk A, and Nieuwland R. Microparticles in cardiovascular diseases. *Cardiovasc Res* 59: 277–287, 2003.
87. Varadhachary AS, Monestier M, and Salgame P. Reciprocal induction of IL-10 and IL-12 from macrophages by low-density lipoprotein and its oxidized forms. *Cell Immunol* 213: 45–51, 2001.
88. Warkentin TE, Hayward CP, Boshkov LK, Santos AV, Sheppard JA, Bode AP, and Kelton JG. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood* 84: 3691–3699, 1994.
89. Watson AD, Navab M, Hama SY, Sevanian A, Prescott SM, Stafforini DM, McIntyre TM, Du BN, Fogelman AM, and Berliner JA. Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. *J Clin Invest* 95: 774–782, 1995.
90. Watson AD, Leitinger N, Navab M, Faull KF, Horkko S, Witztum JL, Palinski W, Schwenke D, Salomon RG, Sha W, Subbanagounder G, Fogelman AM, and Berliner JA. Structural identification by mass spectrometry of oxidized phospholipids in minimally oxidized low density lipoprotein that induce monocyte/endothelial interactions and evidence for their presence in vivo. *J Biol Chem* 272: 13597–13607, 1997.
91. Watson RW, Rotstein OD, Nathens AB, Parodo J, and Marshall JC. Neutrophil apoptosis is modulated by endothelial transmigration and adhesion molecule engagement. *J Immunol* 158: 945–953, 1997.
92. Welch JS, Ricote M, Akiyama TE, Gonzalez FJ, and Glass CK. PPARgamma and PPARdelta negatively regulate specific subsets of lipopolysaccharide and IFN-gamma target genes in macrophages. *Proc Natl Acad Sci U S A* 100: 6712–6717, 2003.
93. Willis D. Expression and modulatory effects of heme oxygenase in acute inflammation in the rat. *Inflamm Res* 44 Suppl 2: S218–S220, 1995.
94. Willis D, Moore AR, Frederick R, and Willoughby DA. Heme oxygenase: a novel target for the modulation of the inflammatory response. *Nat Med* 2: 87–90, 1996.
95. Willoughby DA, Moore AR, Colville-Nash PR, and Gilroy D. Resolution of inflammation. *Int J Immunopharmacol* 22: 1131–1135, 2000.

96. Wun T, Paglieroni T, and Holland P. Prolonged circulation of activated platelets following plasmapheresis. *J Clin Apheresis* 9: 10–16, 1994.
97. Yamada Y, Stafforini DM, Imaizumi T, Zimmerman GA, McIntyre TM, and Prescott SM. Characterization of the platelet-activating factor acetylhydrolase from human plasma by heterologous expression in *Xenopus laevis* oocytes. *Proc Natl Acad Sci U S A* 91: 10320–10324, 1994.
98. Zwaal RF and Schroit AJ. Pathophysiologic implications of membrane phospholipid asymmetry in blood cells. *Blood* 89: 1121–1132, 1997.

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3. Boon C. Heng, Catherine M. Cowan, Dariush Davalian, John Stankus, Duc Duong-Hong, Kevin Ehrenreich, Shubhayu Basu. 2009. Electrostatic binding of nanoparticles to mesenchymal stem cells via high molecular weight polyelectrolyte chains. *Journal of Tissue Engineering and Regenerative Medicine* **3**:4, 243-254. [CrossRef]
4. Alexandra Kadl, Elena Galkina, Norbert Leitinger. 2009. Induction of CCR2-dependent macrophage accumulation by oxidized phospholipids in the air-pouch model of inflammation. *Arthritis & Rheumatism* **60**:5, 1362-1371. [CrossRef]
5. Shane R. Thomas , Paul K. Witting , Grant R. Drummond . 2008. Redox Control of Endothelial Function and Dysfunction: Molecular Mechanisms and Therapeutic OpportunitiesRedox Control of Endothelial Function and Dysfunction: Molecular Mechanisms and Therapeutic Opportunities. *Antioxidants & Redox Signaling* **10**:10, 1713-1766. [Abstract] [PDF] [PDF Plus]
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7. Gerhard Krönke, Norbert Leitinger. 2006. Oxidized phospholipids at the interface of innate and adaptive immunity. *Future Lipidology* **1**:5, 623-630. [CrossRef]
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9. Colin H Macphee, Jeanenne J Nelson, Andrew Zalewski. 2005. Lipoprotein-associated phospholipase A2 as a target of therapy. *Current Opinion in Lipidology* **16**:4, 442-446. [CrossRef]
10. HESTER A. DOYLE, MARK J. MAMULA. 2005. Posttranslational Modifications of Self-Antigens. *Annals of the New York Academy of Sciences* **1050**:1, 1-9. [CrossRef]
11. Valerian E. Kagan , Peter J. Quinn . 2004. Toward Oxidative Lipidomics of Cell SignalingToward Oxidative Lipidomics of Cell Signaling. *Antioxidants & Redox Signaling* **6**:2, 199-202. [Abstract] [PDF] [PDF Plus]