Sol Sherry Lecture in Thrombosis
Molecular Events in Acute Inflammation

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Abstract—The inflammatory response is characterized by a multistep molecular interaction between “signaling” cells, such as endothelial cells, and “responding” cells, such as neutrophils and monocytes. In the first step, selectins produced by signaling cells mediate the tethering of responding cells at sites of inflammation. Subsequently, an additional mediator expressed by signaling cells activates the tethered responding cells. Under pathological conditions, the same mechanism is invoked in inappropriate ways: (1) by prolonged presentation of selectins on the cell surface and (2) by the unregulated production of oxidized phospholipids that mimic the normal secondary signaling molecule, platelet-activating factor (PAF). The enzyme PAF acetylhydrolase (PAF-AH) inactivates PAF and oxidized phospholipids and constitutes an “off” switch that suppresses inflammation. Inhibition of normal PAF-AH function or inactivating mutations of the PAF-AH gene can lead to increased susceptibility to inflammatory disease. These studies have relevance to atherosclerosis and thrombosis, because inflammation is a central feature of both. (Arterioscler Thromb Vasc Biol. 2002;22:727-733.)

Key Words: inflammation ■ selectins ■ platelet-activating factor ■ chemokines ■ oxidized phospholipids

This article is a summary of the Sol Sherry lecture of the Council on Arteriosclerosis, Thrombosis, and Vascular Biology, which was presented at the 73rd Scientific Sessions of the American Heart Association, New Orleans, La, November 12–15, 2000. It highlights work from our laboratory addressing the molecular basis of inflammation, particularly early events at the vascular wall. For this lecture, we have focused on our own work and have not attempted to provide a general review of this topic.

In response to infection and other tissue damage, leukocytes emigrate from the bloodstream to the tissues. The adhesion of leukocytes to endothelial cells is a crucial first step in this process. When appropriately regulated, the inflammatory response is physiological and homeostatic. However, when the stimulus is spatially, temporally, or quantitatively inappropriate, adhesion and activation of leukocytes can have pathological effects (Figure 1). We have focused on the molecular changes responsible for these early steps. We have described a mechanism by which cells react to inflammatory signals to permit a spatially specific response and a high-fidelity reaction (Figure 2). Several different types of circulating cells use this same molecular mechanism.

“Signaling” cell/“responding” cell pairs of a number of different types are involved in inflammatory events, eg, endothelial cells and polymorphonuclear neutrophils (PMNs), endothelial cells and monocytes, and platelets and monocytes. We and others (see review1) have shown that in all of these cases, the signaling cell communicates with the responding target cell in a multistep fashion. First, it tethers the target cell at the site of inflammation, and then it sends a signal to it through a molecule recognized by a receptor on the target cell, often in a juxtacrine fashion. The target cell responds by eliciting new cellular behaviors, including, in some cases, altered gene transcription.

In the case of the immediate inflammatory response between PMNs and endothelial cells, the initial adhesion is mediated by P-selectin. On appropriate stimulation by agonists, P-selectin stored within endothelial cells is rapidly translocated to the cell surface. As a result, the surface of endothelial cells is altered from a nonadhesive and nonthrombogenic character to a proadhesive surface. P-selectin binds to counterreceptors, such as P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes, tethering leukocytes to the activated endothelial cells. Quantitative analyses show that P-selectin is only transiently expressed on the surface of activated endothelial cells2 and that the bulk is reinternalized with 30 minutes of agonist exposure.3

A subsequent step consists of activation of the tethered leukocytes by an additional signal from the activated endothelial cells. This is accomplished by the production of platelet-activating factor (PAF) by the endothelial cell and its expression on the cell surface. Leukocytes express a receptor for PAF that potently induces a program of adhesion and β-integrin–mediated migration by the leukocyte. PAF also...
primes leukocytes for agonists that they will encounter after the leukocytes migrate out of the vasculature.

The multistep process has several advantages. First, the fact that the initiating signal is expressed on the surface of the endothelial cell means that the signal is fixed in space. One implication of this model is that the local concentration of the activating mediator could be very high, despite a low systemic concentration. As a result, leukocytes are recruited precisely where they are needed. Second, the initial “tethering without activating” step permits an editing function by the PMN. Binding to P-selectin brings the PMN into proximity with the endothelial cell, permitting the PMN to scan for an activating signal. If such a signal is present, the PMN is activated and expresses integrins to augment the adhesive response. If no activator is present, the leukocyte is released and reenters the circulation. Tethering is the molecular basis for the observation that leukocytes roll on the endothelium in vivo.

Various types of molecules participate as mediators of immediate versus delayed (ie, requiring >1 hour to become evident) inflammatory responses. However, the general principle of the response is similar. In both cases, endothelial cells are stimulated to express members of the selectin family of adhesion molecules that then bind constitutively expressed counterreceptors on circulating leukocytes. The specific molecules and the manner in which each species is expressed account for the observed temporal differences between immediate and delayed inflammatory processes.

Several features differentiate delayed from immediate responses. In more delayed adhesive responses, activated endothelial cells use E-selectin as a tether, and the secondary activating molecule is a chemokine, such as interleukin-8 (IL-8). In this case, E-selectin is not previously stored in unstimulated endothelial cells. Instead, agonists such as tumor necrosis factor (TNF) transcriptionally activate the E-selectin gene in a highly regulated manner, a process that results in E-selectin accumulation within a few hours. Surface expression of E-selectin reaches a maximum within 12 hours and typically returns to basal levels by 24 hours. The second signaling molecule in the stepwise process is also synthesized in response to inflammatory stimuli. Thus, the expressions of tethering and activating molecules occur in parallel. The time required for the expression and accumulation of each signaling protein affects the temporal readout of delayed inflammatory responses. An additional molecular difference is that PAF is cell-associated, whereas IL-8 is released from activated endothelial cells as a soluble molecule. This could theoretically result in widespread inflammation. However, surface receptors expressed by endothelial cells specifically bind IL-8, which serves to localize the response to discrete areas of the vasculature.

Monocyte Cytokine Secretion Is Regulated by P-Selectin Tethering and PAF Signaling

Cell-cell interactions at vascular interfaces may establish levels or patterns of immediate-early gene expression. In fact, it is known that contact between monocytes and stimulated endothelial cells is a critical control point in inflammation, particularly in atherosclerosis. In our studies of cell-cell interactions that influence signaling by cytokines, we showed that monocytes adherent to either purified P-selectin or to P-selectin–transfected Chinese hamster ovary cells secrete cytokines, such as monocyte chemotactic protein (MCP)-1 and TNF-α, in response to stimulation by PAF.

To explore the mechanism by which adhesion to P-selectin influences cytokine gene expression in monocytes, we focused on the effect of adhesion on nuclear factor-κB (NF-κB), a transcription factor. NF-κB is a key regulator of immediate-early genes in monocytes and is required for MCP-1 and TNF-α expression. We found that the adhesion

Figure 1. Physiological (A) and dysregulated (B) inflammation are mediated by leukocyte adhesion to the vascular wall in response to a variety of stimuli.

Figure 2. P-selectin and PAF expressed by endothelial cells provide a physiological mechanism for temporally and spatially regulated leukocyte recruitment.
of monocytes to purified immobilized P-selectin caused a small but consistent translocation of NF-κB to the nucleus. This nuclear translocation was enhanced dramatically when the cells were stimulated with PAF. This suggests that facilitated transfer of NF-κB may be a mechanism by which adhesion to P-selectin amplifies MCP-1 and TNF-α secretion by stimulated monocytes. Thus, monocyte adhesion to P-selectin presented by stimulated endothelial cells or by platelets can potentially influence cytokine generation early in inflammatory processes. Furthermore, the concerted expression of PAF can dramatically augment this response.

Molecules Required for Activated Platelets to Adhere to and Signal Human Monocytes

To understand the inflammatory responses associated with the simultaneous recruitment of platelets and leukocytes, we identified the functional alterations induced when monocytes bind to the surface of activated platelets. The activation of platelets by thrombin, PAF, oxidized phospholipids (OxPLs), and other agonists leads to the adhesion of monocytes to the platelets, intercellular signaling, altered gene expression, and synthesis of mediators. In turn, monocytes engage adhesion molecules that tether these cells and that induce intracellular signals delivered through surface receptors.

When they are activated in vivo, endothelial cells and platelets translocate P-selectin to the surface from intracellular storage granules. Monocytes adhere to both cell types. Endothelial cells express P-selectin transiently under most physiological conditions. In contrast, platelets express P-selectin in a relatively stable manner and can sustain platelet-monocyte contact for hours. We asked whether the binding of monocyte PSGL-1 to P-selectin presented on activated human platelets affects nuclear signaling or chemokine generation by the leukocytes. This issue is important because monocytes and platelets adhere to one another in numerous inflammatory and thrombotic disorders. As previously shown, when monocytes were mixed with thrombin-activated platelets, adhesion between the 2 types of cells resulted. In addition, activated platelets formed “rosettes” around several monocytes. To determine whether the adherent platelets induced chemokine release by the monocytes, we coincubated the 2 cell types and monitored release of the chemokine MCP-1. Platelets activated by thrombin induced significant release of MCP-1 compared with control levels. Chemokine secretion was dependent on P-selectin expression, inasmuch as neutralization of P-selectin with a specific blocking antibody significantly attenuated MCP-1 secretion and inhibited rosette formation in platelet-monocyte mixtures.

Complementary experiments have shown that chemokine secretion is dependent on the presence of PSGL-1. P-selectin preferentially binds to PSGL-1, a sialomucin that is constitutively present on monocytes and other myeloid leukocytes. We used a monoclonal antibody that recognizes PSGL-1 and blocks its binding to P-selectin, and we found that blocking this interaction inhibits platelet-monocyte rosette grouping and MCP-1 secretion by monocytes. Thus, the expression of P-selectin and also of PSGL-1 is required for these responses to occur.

To establish whether the binding of P-selectin to PSGL-1 is sufficient for activated platelets to induce chemokine secretion by monocytes, we used a similar system, ie, endothelial cells and PMNs. These experiments showed that platelets must express an additional component for platelet-monocyte signaling to take place. The activating molecule was identified as RANTES, a C-C chemokine originally detected in activated T lymphocytes that is released by activated platelets and regulates MCP-1 secretion by monocytes. RANTES is stored and then secreted from platelets stimulated with thrombin; a cell surface receptor for RANTES is found on monocyctic cells. Thus, signaling that arises from platelet-monocyte interactions is similar to that following endothelial cell–neutrophil adhesion in that both require expression of P-selectin by the signaling cell. In neither case, however, is this sufficient. Expression of a second molecule, PAF or RANTES, for endothelial cells and platelets, respectively, is necessary for the completion of the signal.

Studies of the role of RANTES as a platelet-derived signal for monocytes have shown that this chemokine is present in substantial amounts in the supernatants from activated platelets and that MCP-1 release in platelet-monocyte suspensions is inhibited by an antibody against RANTES. Because the antibody did not block the formation of platelet-monocyte aggregates, RANTES-induced signaling apparently occurs after the binding event. However, induction of MCP-1 involved the expression of P-selectin and also of RANTES, inasmuch as monocytes cultured on albumin rather than P-selectin showed no induction of MCP-1 secretion when treated with RANTES.

MCP-1 was not the only monocyte chemokine induced by exposure to activated platelets. IL-8, a C-X-C chemokine that is a potent neutrophil chemoattractant, was released by monocytes incubated with activated platelets but not by monocytes cultured alone or with unstimulated platelets. We found that IL-8 secretion was induced when monocytes that had adhered to purified immobilized P-selectin were stimulated with RANTES but was not induced on control surfaces coated with albumin or fibronectin. Thus, the formation of platelet-monocyte aggregates results in the production of a variety of potent chemokine effectors.

Pathological Activation

Oxidants and free radicals are deleterious in many ways, and organisms use numerous approaches to block their production and limit their damage. Many oxidative chemical reactions are not constrained by enzymes and may show exponential reaction rates. Some products of oxidative attacks, including those of lipid oxidation, are highly reactive species that modify proteins and DNA or activate components of the immune and inflammatory systems. Such changes are thought to be important in the pathogenesis of atherosclerosis and other diseases.

We have studied the characteristics and actions of OxPLs that are involved in inflammatory stimulation. To approach this question, we subjected human endothelial cells to oxidative stress by exposing them to low concentrations (100 to 200 μmol/L) of oxidants, such as H2O2 and tert-butylhydroperoxide. We found that PMNs adhered to treated...
endothelial cells and that this adhesion was blocked entirely by antibodies to P-selectin. We observed that the time course of P-selectin expression by cells subjected to oxidative stress was different from that by cells treated with physiological stimuli. P-selectin remained on the surface of oxidized endothelial cells for hours compared with its transient appearance on cells treated with thrombin or histamine. This lack of regulation of P-selectin expression by endothelial cells exposed to oxidants is likely to have important implications in pathological inflammation.

In addition to our findings in P-selectin expression, we observed a dramatic alteration of the morphology of endothelial cells exposed to oxidants. A time-dependent vesiculation, or “blebbing,” of the plasma membrane occurred, and many vesicles were shed into the supernatant. In contrast to buffer-treated controls, supernatants from oxidant-treated endothelial cells caused PMNs to adhere to gelatin-coated plates, a response that required integrin activation. The vesicles contained little, if any, P-selectin, as determined by immunoblot assay.

We explored further the identity of the oxidant-induced activating agent. We had found previously that synthetic phosphatidylcholine is fragmented by oxidation, generating analogs of PAF. In related experiments, we demonstrated that oxidatively fragmented phosphatidylcholines activated neutrophils, a response that was inhibited by specific antagonists of the PAF receptor. We hypothesized that the exposure of endothelial cells to strong oxidants might generate oxidatively fragmented phospholipids with PAF-like biological activity. In subsequent experiments, we showed this to be the case and identified the active component as a phospholipid that caused adhesion of neutrophils by functional upregulation of CD11/CD18 integrins. Competitive antagonists of the PAF receptor completely blocked neutrophil adhesion induced by these OxPLs. We examined the possibility that the vesicles contained authentic PAF but, in an extensive set of experiments, found little or none.

To physically characterize the bioactive phospholipid, we separated vesicular lipids by high-performance liquid chromatography. Fractions were assayed for their ability to stimulate neutrophil adhesion. The stimulatory material that we identified did not comigrate with authentic PAF and was identical to fractions that we had previously shown to contain the free radical–catalyzed oxidation products of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine. Like PAF, the phospholipids we identified were hydrolyzed by PAF acetylhydrolase (PAF-AH), a phospholipase A2 that attacks only phospholipids we identified were hydrolyzed by PAF acetylhydrolase (PAF-AH), a phospholipase A2 that attacks only phospholipids with shortened sn-2 residues. Some of these oxidation products, termed “PAF-like” phospholipids, are able to activate cells expressing the PAF receptor, including monocytes, leukocytes, and platelets. Because oxidation of phosphatidylcholines generates a plethora of chemically related molecules and because only some of these stimulate the PAF receptor, identification of the specific biologically active species has been complicated. We have found that oxidation of very rare phosphatidylcholine species in LDL generates all of the bioactive PAF receptor agonists derived from LDL oxidation.

In summary, we have found that oxidant-exposed endothelium sheds vesicles that contain potent activators of neutrophil function. The active compounds are phospholipids that have been oxidatively fragmented to yield structural analogs of PAF. In contrast to PAF synthesis, which is carefully controlled, the formation of potent mimetics after oxidation of synthetic phosphatidylcholines, isolated LDLs, and foodstuffs is unregulated. Therefore, these oxidative reactions have the potential to produce high concentrations of potent inflammatory agents. Endothelial cells transiently synthesize PAF in response to physiological agonists but do not release it. In contrast, oxidant-treated endothelial cells release PAF-like phospholipids, which may spread tissue damage from the immediate area to other organs. The production of oxidatively fragmented phospholipids is not regulated by the usual constraints on synthesis. Thus, degradation represents a crucial mechanism necessary to suppress the actions of these toxic products. Indirect evidence supporting the notion that PAF-like lipids have pathological effects includes the fact that deficiency of PAF-AH is correlated with an increased risk of stroke and increased levels of circulating PAF-like lipids.

In Vivo Tests of OxPLs as Inflammatory Agents

Because the oxidative reactions that create PAF-like lipids were all performed in a laboratory setting, it was not known whether sufficiently oxidizing conditions exist in vivo to create the inflammatory PAF mimetics that we had studied. It was also not known whether such mediators could accumulate to effective levels in the face of plasma antioxidants and endogenous defense mechanisms, such as the constitutively active PAF-AH. On the basis of these considerations, we and others sought to determine whether cigarette smoke could elicit the accumulation of PAF-like lipids in an intact organism and whether these compounds constitute the circulating mediators responsible for inflammatory changes observed after cigarette smoke exposure. If this were the case, simple antioxidant protection might suppress the accumulation of toxic oxidation products, thereby suppressing the proinflammatory effects of smoking.

To address these issues, we first isolated polar lipids from the plasma of hamsters exposed to the smoke of 1 reference cigarette and tested the ability of these lipids to promote neutrophil adhesion. These experiments showed that lipids from treated, but not control, plasma exerted a marked adhesion-promoting effect. The stimulatory material was eluted in fractionation experiments with the same profile as polynsaturated fatty acids, yielding a large series of phosphatidylcholines with shortened sn-2 residues. Some of these oxidation products, termed “PAF-like” phospholipids, are able to activate cells expressing the PAF receptor, including monocytes, leukocytes, and platelets. Because oxidation of phosphatidylcholines generates a plethora of chemically related molecules and because only some of these stimulate the PAF receptor, identification of the specific biologically active species has been complicated. We have found that oxidation of very rare phosphatidylcholine species in LDL generates all of the bioactive PAF receptor agonists derived from LDL oxidation.
OxPLs with PAF-like activity. The biological activity of the smoke-induced inflammatory agonists was equivalent to \(10^{-7}\) mol/L PAF per milliliter plasma. The effect of these lipids could be blocked with a specific competitive antagonist to the PAF receptor. Thus, in vivo stimulation of OxPL production by exposure to cigarette smoke was effective in inducing inflammatory cell adhesion.

To further understand the mechanism of action of PAF-like lipids, we visualized leukocyte interaction with the microvascular endothelium in response to cigarette smoke. We found that smoke-induced leukocyte adherence to arteriolar and venular endothelium was significantly inhibited by pretreating the animals with a highly selective PAF receptor antagonist or by blocking the PAF receptor before smoke exposure.

In addition to leukocyte–endothelial cell interactions, we observed rapid formation of circulating leukocyte-platelet aggregates in hamsters exposed to cigarette smoke. Experiments showed that PAF-like lipids extracted from the plasma of smoke-exposed hamsters were responsible for this aggregation formation. A characteristic feature of monocyte-platelet aggregates that is not shown by individual monocytes is their enhanced ability to synthesize and secrete inflammatory cytokines that attract and activate monocytes (C-C family, eg, MCP-1) and neutrophils (C-X-C family, eg, IL-8). We found that in the presence of platelets, PAF-like lipids induce substantial synthesis of MCP-1 and IL-8 by monocyte-platelet aggregates compared with controls. These data suggest that PAF-like lipids amplify the inflammatory response, inasmuch as they induce the synthesis of inflammatory cytokines by circulating platelet-monocyte aggregates.

We next sought to determine whether antioxidants prevent the accumulation of PAF-like lipids that mediate the inflammatory reaction induced by cigarette smoke. We fed the antioxidant vitamin C to hamsters and then extracted and purified PAF-like lipids from the animals after exposure to smoke. We measured the amount of stimulatory activity in these extracts relative to maximally effective levels of PAF. We found that exposure to cigarette smoke results in the accumulation of significant levels of circulating PAF-like lipids and that vitamin C pretreatment reduces the amount of these lipids to background levels.

The work mentioned above demonstrated for the first time that PAF-like lipids are formed and accumulate in vivo. Characterization of these modified phospholipids shows that the biological activity falls within an order of magnitude of that of PAF. Thus, the results from our in vivo and in vitro approaches have demonstrated that PAF-like lipids generated in the plasma of hamsters exposed to cigarette smoke act as the primary mediators of subsequent microvascular events.

**Regulation of PAF-Mediated Effects**

PAF mediates a wide range of immune and allergic reactions. If the mechanism for inactivation of PAF is impaired, effector cells may be recruited to sites of injury for inappropriately long times, resulting in prolonged inflammation. There are several powerful mechanisms that, individually or together, can control the biological activities of PAF under physiological conditions. These include regulation of the expression and activity of the receptor, tightly controlled pathways for PAF synthesis, regulation of the presentation of PAF by juxtacrine signaling, and efficient degradative enzymes, the PAF-AHs. There are several forms of PAF-AH activities, both intracellular and secreted. These enzymes are constitutively active and are calcium independent (Figure 3).

The plasma form of PAF-AH plays a key role as a scavenger of PAF and OxPLs. We have characterized the human plasma PAF-AH and cloned its cDNA. The enzyme is inactive against long-chain phospholipids, a property that explains its ability to circulate in active form without acting on lipids that constitute blood cell membranes and lipoproteins. In addition to PAF, a second group of compounds hydrolyzed by PAF-AH, the oxidatively fragmented phospholipids, also have short and/or oxidized ayl groups at the sn-2 position of glycerol.

In contrast to the synthesis of PAF, which is highly regulated, OxPLs are produced in an uncontrolled manner. The extent to which products of phospholipid oxidation accumulate depends heavily on the rate at which they are catabolized. Inasmuch as PAF-AHs are maximally active in the basal state and do not require calcium for activity, they provide an immediate defense mechanism against toxic effects mediated by fragmented phospholipids.

PAF provokes inflammation in part by its ability to activate PMNs, resulting in changes required for the directional migration of cells. We found that preincubation of PAF with recombinant PAF-AH caused PAF to lose its ability to activate cell polarization and cell spreading in vitro. PAF is also a potent stimulus for increased permeability of the vasculature, a prominent component of severe inflammation. Using the well-characterized paw edema model, we found that pretreatment of the footpads with recombinant PAF-AH blocked PAF-induced edema by >85%. Similarly, intravenous pretreatment with recombinant PAF-AH blocked PAF-induced footpad edema by >80%. We also tested PAF-AH in a pleurisy model characterized by vascular leakage into the pleural space in response to PAF. Rats were pretreated with either recombinant PAF-AH or control buffer, and then PAF was injected into the pleural space. One hour later, the degree of vascular leakage was determined. Compared with control animals, the rats that received PAF-AH had a >80% reduction of vascular leakage. Collectively, the in vivo and in vitro
results demonstrate that PAF-AH abolishes the inflammatory effects of PAF on leukocytes and the vasculature.

Many studies have examined the possibility that deficiency of the plasma form of PAF-AH is associated with inflammatory disease. Inasmuch as the secreted enzyme can control the magnitude and duration of PAF-mediated signaling, a decreased ability to degrade PAF would be predicted to result in pathological responses. Studies from other laboratories have shown that the activity of plasma PAF-AH is decreased in patients with asthma, systemic lupus erythematosus, and septic shock. Our results have shown that the administration of supplemental exogenous PAF-AH suppresses inflammation in vivo. Thus, in diseases in which there is a deficiency of enzyme activity, PAF or related compounds may accumulate in vivo. Thus, in diseases in which there is a deficiency of supplemental exogenous PAF-AH suppresses inflammation. These studies have important netic or environmental causes leads to an increased susceptibility to inflammatory disease. Inactivation of PAF-AH by genetic or environmental factors increases susceptibility to inflammatory and allergic diseases, demonstrating that PAF-AH functions as an anti-inflammatory safety net.

Conclusions
A multistep molecular interaction occurs when cells are activated by inflammatory agents. Activated cells tether responding cells through the expression of selectins. Activation of responding cells occurs by means of a second type of molecule expressed by the signaling cell. In endothelial cell–PMN interactions, P-selectin is the tether, and the lipid PAF is the activating molecule. Under pathological conditions, this same stepwise mechanism is invoked in inappropriate ways, first by prolonged expression of P-selectin and then by the unregulated production of OxPLs that mimic the actions of PAF. PAF-AH acts as an off signal for PAF and also for OxPL because it inactivates these lipids, thereby suppressing inflammation. Inactivation of PAF-AH by genetic or environmental causes leads to an increased susceptibility to inflammatory disease. These studies have important implications in the pathogenesis of disease with components of inflammation, such as atherosclerosis and other vascular syndromes.

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References


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