Effects of Oxidized Low Density Lipoprotein, Lipid Mediators and Statins on Vascular Cell Interactions

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The integrin heterodimer CD11b/CD18 (αMβ2, Mac-1, CR3) expressed on monocytes or polymorphonuclear leukocytes (PMN) is a receptor for iC3b, fibrinogen, heparin, and for intercellular adhesion molecule (ICAM)-1 on endothelium, crucially contributing to vascular cell interactions in inflammation and atherosclerosis. In this report, we summarize our findings on the effects of lipid mediators and lipid-lowering drugs. Exposure of endothelial cells to oxidized low density lipoprotein (oxLDL) induces upregulation of ICAM-1 and increases adhesion of monocytes expressing Mac-1. Inhibition experiments show that monocytes use distinct ligands, i.e. ICAM-1 and heparan sulfate proteoglycans for adhesion to oxLDL-treated endothelium. An albumin-transferable oxLDL activity is inhibited by the antioxidant pyrrolidine dithiocarbamate (PDTC), while 8-epi-prostaglandin F2α (8-epi-PGF2α) or lysophosphatidylcholine had no effect, implicating yet unidentified radicals. Sequential adhesive and signaling events lead to the firm adhesion of rolling PMN on activated and adherent platelets, which may occupy areas of endothelial denudation. Shear-resistant arrest of PMN on thrombin-stimulated platelets in flow conditions requires distinct regions of Mac-1, involving its interactions with fibrinogen bound to platelet αIIbβ3, and with other platelet ligands. Both arrest and adhesion strengthening under flow are stimulated by platelet-activating factor and leukotriene B4, but not by the chemokine receptor CXCR2. We tested whether Mac-1-dependent monocyte adhesion is affected by inhibitors of hydroxy-methylglutaryl-Co-enzyme A reductase (statins) which improve morbidity and survival of patients with coronary heart disease. As compared to controls, adhesion of isolated monocytes to endothelium ex vivo was increased in patients with hypercholesterolemia. Treatment with statins decreased total and low density lipoprotein (LDL) cholesterol plasma levels, surface expression of Mac-1, and resulted in a dramatic reduction of Mac-1-mediated monocyte adhesion to endothelium. The inhibition of monocyte adhesion was reversed by mevalonate but not LDL in vitro, indicating that isoprenoid precursors are crucial for adhesiveness of Mac-1. Such effects may crucially contribute to the clinical benefit of statins, independent of cholesterol-lowering, and may represent a paradigm for novel, anti-inflammatory mechanisms of action by this class of drugs.

Key words: Adhesion; Endothelium; Lipids; Monocytes; Platelets.

Monocyte Adhesion to Oxidized Low Density Lipoprotein-Stimulated Endothelium Mediated by Distinct Ligands

The process of atherogenesis involves the actions of oxidized low density lipoprotein (oxLDL). An extensive oxidative modification of LDL may occur in an antioxi-

dant-depleted subendothelial microenvironment (1). OxLDL can induce the initial adhesiveness and transmi-
gation of human blood monocytes or monocytic cell lines on vascular endothelium, possibly enhancing monocyte recruitment and retention (2–5). In addition, stimulation of endothelial cells with oxLDL has been re-
ported to increase adhesion of human blood monocy-
tes (6). However, the mechanisms involved in this ef-
fect remain to be completely elucidated. Studies in human umbilical vein endothelial cells (HUVEC) have demonstrated that intercellular adhesion molecule (ICAM)-1 expression is upregulated by oxLDL or by long-term incubation with native LDL (6, 7). Two novel endothelial adhesion proteins for monocytic cells have recently been described to be induced by minimally modified LDL (mmLDL) (8, 9). We have shown that the human monocytic cell line Mono Mac 6 (10) is an appropri-
ate in vitro tool to study monocyte interactions with cytokine-stimulated endothelium (11). In the fol-
lowing section, we have summarized findings on the adhesion of Mono Mac 6 cells to oxLDL-stimulated HU-
VEC, in an attempt to characterize the endothelial ligands involved in this interaction and to identify responsible active components in the oxLDL prepara-
tions used.

Treatment of HUVEC with oxLDL for 24 hours dose-
dependently increases the adhesion of human mono-
cytic Mono Mac 6 cells but not of U937 cells. Mac-1 (CD11b/CD18), a monocytic counter-receptor for ICAM-
1 that also binds to heparin (12), is present on Mono 
Mac 6 but not U937 cells, and may thus explain these differences in adhesion (11). Consistently, oxLDL in-
duces a two-fold upregulation of ICAM-1 but not vas-

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cell adhesion molecule (VCAM)-1 or E-selectin surface expression on HUVEC. Maltose-1-phosphate (M1P) or heparin but not monoclonal antibodies (mAbs) to ICAM-1 reduce Mono Mac 6 cell adhesion to untreated HUVEC. Induction of unidentified endothelial cell adhesion molecule (mAbs) to ICAM-1 with either M1P or heparin, a recently identified Mac-1 ligand (12), inhibited Mono Mac 6 adhesion to oxLDL-stimulated HUVEC by more than 50%, while either alone had no effect. This suggests that two distinct endothelial ligands for Mac-1, inducible ICAM-1 and heparan sulfate proteoglycans, mediate monocyte interaction with oxLDL-treated HUVEC. The composition of oxLDL particles is subjected to considerable variation (1). Our preparations are thoroughly washed in EDTA-containing phosphate buffer saline (PBS) after oxidation, comparable to dialyzing. Consistently, toxic effects (e.g. lactate dehydrogenase (LDH) elevation or detachment) are detectable after 24 hours incubation of HUVEC with unwashed but not washed oxLDL. The extraction of oxLDL components by treatment with bovine serum albumin (BSA) and subsequent separation results in diminished activity of oxLDL and a transfer of active components to BSA, as indicated by the induction of ICAM-1 expression and monocyte adhesion. However, candidate lipid peroxidation products, lyso-phosphatidylcholine (LPC) or 8-epi PGF2α, have not been identified yet. The change in the activity of ICAM-1 upregulation. Consistently, recent studies in a rat model have shown that the injection of LDL is associated with the appearance of vascular reactivity for oxLDL epitopes and endothelial ICAM-1 expression on endothelium after 24 hours (18). In addition, expression of ICAM-1 on endothelium subsequently serves to support dynamically regulated and lymphocyte function associated-1 (LFA-1)-mediated transmigration of monocytes (Figure 1), e.g. in response to monocyte chemotactic protein-1 (MCP-1) (19).

A clear inhibition of monocyte adhesion to oxLDL-stimulated HUVEC with ICAM-1 mAbs requires their combination with M1P or heparin, indicating an essential involvement of at least two distinct endothelial ligands in increased monocyte adhesion. i.e. ICAM-1 following initial upregulation by oxLDL and heparan sulfate proteoglycans (16). Consistently, ICAM-1 mAb only slightly inhibits monocyte adhesion to oxLDL-treated vascular smooth muscle cells despite induction of ICAM-1, and blocking one endothelial ligand marginally affects monocyte binding to cytokine-stimulated HUVEC, whereas combinations of mAbs cause strong inhibition (20, 21), indicating that alternative ligands can compensate for blocking one interaction. An inhibition of adhesion with M1P in combination with ICAM-1 mAbs suggests a contribution of ligands for monocytes, which are also induced by mmLDL and can be blocked with M1P (14). Distinct endothelial ligands induced by mmLDL (8, 9) do not appear to be identical with such ligands (16), since they mediate U937 adhesion, which is not increased by oxLDL. An inhibition of monocyte adhesion with the soluble Mac-1 ligand heparin (12) indicates that cellular heparan sulfate proteoglycans are involved in monocyte adhesion to untreated HUVEC. While heparin alone has no effect, combining heparin with ICAM-1 mAbs significantly inhibits monocyte adhesion to oxLDL-stimulated HUVEC. This indicates that, in addition to ICAM-1, the presence of such heparan sulfate proteoglycans is required to mediate monocytes cell adhesion to oxLDL-stimulated HUVEC, emphasizing the involvement of at least two distinct li-
gands. Heparin can release and neutralize heparan-bound chemokines such as growth-stimulating activity (GRO), but not MCP-1, both of which are induced by mmLDL and are involved in mediating monocyte adhesion (22, 23). GRO may participate in the heparin-inhibitable adhesion, since heparin inhibits adhesion to untreated endothelium where little GRO is expressed (22). The endothelial ligands for monocytes induced by oxLDL are schematically depicted in Figure 1.

The properties of the oxLDL preparations used appear to resemble those of LDL modified by coincubation with cultured cells (17). In search for active components in oxLDL, we found that physiologically relevant concentrations of 8-epi PGF\(_2\alpha\) (14) do not enhance monocyte adhesion to HUVEC. In contrast to previous studies (15, 24), LPC does not contribute to the effects of oxLDL. This is consistent with results showing that effects of oxLDL are not necessarily mediated by LPC (25). Optimal treatment with LPC requires binding to BSA (24), causing differences in effectiveness. The transfer of active components in oxLDL to BSA indicates the presence of lipophilic oxidation products other than LPC, such as lipid peroxides or radicals, that are responsible for induction of ICAM-1 and monocyte adhesion. This is also supported by the prevention of oxLDL-induced effects with PDTC, a potent radical scavenger (20). Recently, it has been demonstrated that oxLDL activates peroxisome proliferator-activated receptor γ (PPARγ)-dependent transcription through a novel signaling pathway involving scavenger receptor-mediated particle uptake, and two of the major oxidized lipid components of oxLDL, 9-hydroxy octadecadienoic acid (9-HODE) and 13-HODE, have been identified as endogenous activators and ligands of PPARγ (26). Such ligand activation can induce changes characteristic of monocytic differentiation and promote uptake of oxLDL through transcriptional induction of the scavenger receptor CD36 (27). This may be relevant to the signal transduction following activation by oxLDL in endothelial cells, which may be mediated by endothelial CD36 as a receptor binding oxLDL (28).

Taken together, our data suggest that washed oxLDL without cytotoxicity upregulates ICAM-1 on endothelium and induces monocyte adhesion that can be mediated by ICAM-1 and additional endothelial ligands (16). The induction of ICAM-1 and the involvement of heparan sulfate proteoglycans in adhesion could further explain the atherogenic potential of oxLDL and may lead to the development of potential therapeutic strategies in the prevention of atherogenesis.

**Involvement of Platelet-Activating Factor (PAF) and Leukotriene B4 (LTB4) in Leukocyte Arrest on Adherent Platelets**

In attempt to define the process of transendothelial leukocyte extravasation, a multistep model has proposed a sequential involvement of various traffic signal molecules. Selectins initiate tethering and rolling of leukocytes as a prerequisite for their stable arrest due to stimulation of \(\beta_2\) integrins in flow (29, 30). Platelets express P-selectin, which is mobilized from \(\alpha\)-granules to the plasma membrane upon activation, and the \(\beta_2\) integrin ligand ICAM-2 (31–33). Thus, a similar multistep model may apply to the highly efficient accumulation of PMN on surface-adherent platelets under flow. Indeed, rolling and arrest of PMN on activated platelets under flow requires the action of P-selectin and \(\beta_2\) integrins, respectively (34–37). Fibrinogen, a Mac-1 ligand (38, 39) which can bind to activated platelets via \(\alpha I\beta\beta\)3 (40), has been implicated in platelet-PMN interactions in cell suspension or whole blood (41). However, the role of Mac-1 in adherence of PMN in flow and the identity of the \(\beta_2\) integrin ligands mediating PMN arrest on activated platelets in flow remain to be elucidated.

Chemoattractants and CXC chemokines have been shown to stimulate adhesiveness of Mac-1 in PMN (42, 43) and convert selectin-mediated rolling of PMN into firm arrest (29). Interactions of PMN and platelets are required for the production of certain chemokines, and for transcellular leukotriene and arachidonic acid metabolism by lipoxygenases (44). Activated platelets produce chemoattractants, e.g., the lipid mediator leukotriene B4 (LTB4) or the hydrolytic phospholipid product, platelet-activating factor (PAF), which may stimulate PMN integrins. Platelets express the CXC chemokines ENA-78, GRO-\(\alpha\) and \(\beta\)-thromboglobulin, a precursor for neutrophil activating peptide-2 (NAP-2) released from \(\alpha\)-granules and processed by cathepsin G (45–47), which act via the receptor CXCR2 on PMN (48). The receptor for PAF and the CXCR2 differ in signal transduction and coupling to \(G\alpha\) proteins (49). Moreover, lipid mediators but not CXC chemokines are soluble in the plasma membrane, while chemokines but not lipid mediators bind to heparin or proteoglycans. This might lead to a differential role for these chemoattractants in activation of PMN under flow.

We studied the pathways that lead to arrest and firm adhesion of rolling PMN on activated, surface-adherent platelets (50). Stable arrest and adhesion strengthening of PMN on thrombin-stimulated, surface-adherent platelets in flow requires distinct \(Ca^{2+}\)- and \(Mg^{2+}\)-dependent regions of Mac-1 (\(\alpha M\beta 2\)) and involves interactions of Mac-1 with fibrinogen bound to platelets via \(\alpha I\beta\beta\)3. Mac-1 also binds to unidentified ligands on platelets other than ICAM-2, heparin or heparan sulfate proteoglycans, as seen by inhibition with mAbs or peptides, treatment of platelets with heparinase and by using platelets with defective \(\alpha I\beta\beta\)3 from a patient with Glanzmann thrombasthenia (50). Tethering of PMN on platelet ICAM-2 via LFA-1 may facilitate the transition between rolling on selectins and Mac-1-dependent arrest. Chemoattractants and chemokines stimulate the avidity of Mac-1 in PMN (43,44) and may convert selectin-mediated rolling into firm arrest (29). Hence, chemoattractive lipid mediators may play a role in accumulation and adhesion strengthening of PMN on activated platelets in flow. Pretreatment of PMN with the PAF receptor antagonist UK-74,505 (51) results in a dose-dependent inhibition of PMN accumulation (50). The LTB4 receptor antagonist SC-53228 is less po-
tent, while no additive effects are seen with both antagonists over UK-74,505 alone. Likewise, pertussis toxin (PTX) inhibits accumulation and shows little additive effect with UK-74,505, whereas pretreatment with the CXCR2 mAb 10H2 did not inhibit arrest. Similar effects were seen for adhesion strengthening (50). UK-74,505, SC-53228 and pertussis toxin PTX but not CXCR2 mAb reduced the shear resistance of PMN adhesion and increased rolling. Contrasting effects were obtained for spreading of PMN on activated platelets in stasis. Thus, PMN arrest and adhesion strengthening on activated platelets under flow conditions appeared to be stimulated by PAF and, to a lesser extent, LTB4 via PTX-sensitive signaling pathways but not by activation of CXCR2 (50).

It has been intriguing to apply a multistep model to the highly efficient accumulation of PMN on activated, surface-adherent platelets in flow. Rolling mediated by P-selectin is important as a prerequisite for firm attachment, and rolling on activated platelets was rapidly followed by Mac-1 mediated arrest on fibrinogen (50). We suggest that distinct functional regions of Mac-1 contribute to PMN arrest and adhesion strengthening on activated platelets in flow. Seven N-terminal repeats of integrin α subunits have been predicted to fold into a β-propeller structure containing putative Ca²⁺-binding motifs located on the lower face, and the I or inserted domain with a Mg²⁺ at its binding site to be tethered to the top of this structure (52). The arrest of PMN may involve Ca²⁺-dependent regions of Mac-1, in particular a putative β-propeller domain, while the Mg²⁺-dependent regions in the I domain may contribute to PMN arrest on activated platelets. Taken together, Mac-1 may be functionally subdivided into regions which contribute to initial arrest and regions which are required for subsequent shear resistance in flow (50).

Arrest and adhesion strengthening of PMN on platelets in flow appears to be stimulated by the lipid mediators PAF and, to a lesser extent, LTB4, via PTX-sensitive signaling pathways, but not by activation of CXCR2 (50). Several reasons may account for differential effectiveness of platelet chemoattractants during PMN activation in shear flow. Firstly, lipid mediators but not CXC chemokines are soluble in the lipid membrane, whereas chemokines but not lipid mediators can be bound to proteoglycans. The differential binding of chemokines to proteoglycan subpopulations may determine the presence and distribution of chemokines in the cellular microenvironment (53). Thus, PAF or LTB4 may be retained in the platelet plasma membrane by partition, whereas relevant platelet CXC chemokines may not be bound to platelet proteoglycans, and may be washed away under flow. Moreover, PMN enzymes required for processing platelet precursors into active CXC chemokines (47) may not be immobilized and may be removed by flow. This would be consistent with inhibition of adhesion strengthening and spreading by the CXCR2 mAb in stasis but not in flow. Alternatively, the PAF receptor may differ from CXCR2 in its PTX-sensitive signal transduction pathways and coupling to Gα proteins (48), which may enable a more rapid activation of Mac-1 adhesiveness under flow conditions. In parallel, endothelial PAF has been implicated in juxta-crine stimulation of integrin function in PMN tethered through P-selectin on thrombin-stimulated endothelium (54). Although P-selectin itself does not trigger arrest of PMN under flow, it may cooperate with chemo-attractants to stimulate leukocytes (55). It has recently been confirmed that PMN adhesion on immobilized platelets under shear flow requires both a juxtacrine activation mechanism involving PAF and an enhancing signal from P-selectin (56). Finally, Mac-1 and homologous interactions of platelet-endothelial cell adhesion molecule-1 (PECAM-1) may contribute to transmigration of PMN through platelet layers, e.g. towards IL-8, thus completing extravasation (37). Figure 2 illustrates the multistep model with a sequential involvement of signal molecules in the efficient accumulation of neutrophils on adherent platelets under shear flow conditions.

The proposed mechanisms of PMN arrest on activated, adherent platelets contribute to a more elaborate...
definition of the multistep model by demonstrating a differential involvement of integrins, their ligands and of chemoattractive lipid mediators in sequential steps of this process. Interactions between platelets and leukocytes occur at sites of vascular damage, as in hemorrhage. Platelets bind to prothrombotic endothelium and the underlying basement membrane in vascular injury, occupying a position analogous to the endothelium. Binding of PMN to platelets immobilized in a thrombus may facilitate immigration into thrombosed areas, wound healing, tissue repair, or protection from infection, and may contribute to the maintenance of vascular integrity, as well as to its impairment in pathological states. Platelets and PMN indeed colocalize at sites of hemorrhage, vascular grafts, atherosclerotic lesions and myocardial infarction (57-60). Activation of PMN and platelet adhesion occurs after coronary angioplasty and is associated with late clinical events (61). Understanding the mechanisms of PMN accumulation on platelets in flow may thus lead to clinical applications and interventions to influence the consequences of leukocyte-platelet interactions in vascular disease.

**Statins Inhibit Monocyte Adhesiveness in Patients with Hypercholesterolemia**

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) are used in the treatment of hypercholesterolemia. They also improve the survival of patients with coronary heart disease (CHD) and prevent CHD in hypercholesterolemic men (62, 63). However, the clinical benefit of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, such as simvastatin and pravastatin, is not strictly correlated to their lipid lowering effects (62, 64). The action of statins on cellular cholesterol biosynthesis in the liver, blood cells, and vasculature may affect membrane integrity and regulation of membrane-related processes (65) which are associated with changes in multiple cellular functions. Cholesterol precursors, i.e. farnesyl or geranyl pyrophosphates, have been implicated in interactions of proteins and protein anchoring to lipid membranes (66, 67), essentially contributing to receptor-stimulated Ca²⁺-increase, superoxide anion formation, LDL oxidation, eicosanoid synthesis and differentiation in monocytes (68-71). Functional consequences of such effects may be relevant for CHD and atherosclerosis. Monocyte recruitment into the vascular wall is crucial for initiation and progression of atherosclerotic lesions (58). Interaction of the monocyte surface receptor Mac-1 with ICAM-1 has been involved in the adhesion to and migration across endothelium of monocytes, particularly when stimulated (5, 30). Hence, we studied effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on monocyte CD11b surface expression and adhesion to endothelium in vitro, as well as on increased adhesiveness of monocytes (72) isolated from hypercholesterolemic patients before and after cholesterol-lowering treatment, using a recently established ex vivo assay with fixed human endothelial cells (73).

In hypercholesterolemic patients, Mac-1-dependent adhesion of isolated monocytes to fixed endothelium expressing ICAM-1 ex vivo is dramatically increased, as compared to healthy controls. Treatment of these patients with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors lovastatin or simvastatin for 6 weeks decreases total and LDL cholesterol plasma levels, as well as monocyte CD11b surface expression, and results in a substantial reduction of monocyte adhesion to endothelium (74). The regulation of CD11b surface expression is dissociated from adhesive function, which requires its activation (75, 76). Thus, the pronounced decrease in adhesion after treatment with statins appears to be independent of the slight reduction in CD11b expression. Adhesiveness of Mac-1 may rather be mediated by a small subpopulation of molecules undergoing conformational changes in response to stimulation (77). Moreover, treatment of monocytes with lovastatin in vitro dose-dependently reduces surface expression of CD11b on monocytes, and inhibits CD11b-dependent adhesiveness to fixed endothelium of monocytes stimulated with MCP-1. Coincubation with mevalonate, but not LDL, reverses these effects (74), suggesting that early cholesterol precursors but not cholesterol are crucial for adhesiveness of CD11b. Hence, lovastatin may interfere with activation of Mac-1 adhesiveness by chemokines in monocytes, due to decreased availability of isoprenoids.

Monocyte accumulation following adhesion to endothelium and extravasation plays a crucial role in atheroma formation due to a perpetuation of chronic inflammatory reaction and lipid deposition into monocyte-derived foam cells (58). These cells further contribute to the instability and disruption of atherosclerotic plaques by secreting metalloproteases that degrade extracellular matrix constituents, and may thus trigger clinical manifestations of atherosclerosis (78). Isoprenoids posttranslationally modify various proteins and mediate protein-membrane anchoring and interactions of proteins. Some of the isoprenylated proteins identified are small guanosine triphosphate (GTP)-binding proteins of the ras family, such as rac and rho, as well as the γ-subunits of heterotrimeric G-proteins (67). Chemoattractant-receptors are coupled to G-protein heterotrimers, and integrin-dependent binding of leukocytes to endothelium can involve a G-protein regulated activation event (30). Lovastatin has been shown to inhibit Ca²⁺-influx stimulated by G-protein-coupled receptors and localization of ras-like proteins into the membrane of mononuclear cells (68). Expression of a constitutively active form of the GTPase R-ras results in activation of β₁ and β₃ integrin avidity, and inactivation of the GTPase rho suggests its participation in signaling via chemoattractant receptors to trigger activation of Mac-1 (79, 80). Hence, statins may impaire activation of Mac-1 involving small GTPases, or stimulation of G-protein-heterotrimer coupled receptors by MCP-1 or other autocrine chemokines. Alternatively, these drugs may act by interfering with the transport, dimerization or anchoring of Mac-1 in the plasma membrane to maintain its cell surface expression. Statins may affect GTP-bind-
Inhibition of leukocyte adhesion and chemotaxis (73, 82, 83) highlights actions of statins which are not related to their cholesterol lowering effects but may be due to interference with cellular isoprenoid metabolism or prenylation-dependent processes. As summarized in Table 1, other direct vascular effects of statins have emerged, i.e. reduction of platelet aggregation (84), inhibition of smooth muscle cell proliferation and migration (85), upregulation of endothelial NO synthetase (86) and inhibition of metalloprotease secretion (87). Our findings may be crucial for clinical benefits of statins, and may represent a novel anti-inflammatory paradigm for the mechanisms of action by this class of drugs (88), which warrants further detailed investigation with respect to leukocyte biology.

### References


### Table 1

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