Lysolecithin-induced Alteration of Subendothelial Heparan Sulfate Proteoglycans Increases Monocyte Binding to Matrix*

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The cause and consequence of altered proteoglycans in atherosclerosis are poorly understood. To determine whether proteoglycans affect monocyte binding, we studied the effects of heparin and proteoglycan degrading enzymes on THP-1 monocyte adhesion to subendothelial matrix (SEM). Monocyte binding increased about 2-fold after SEM was treated with heparinase. In addition, heparin decreased monocyte binding to fibronectin, a known SEM protein, by 60%. These data suggest that SEM heparan sulfate inhibits monocyte binding to SEM proteins. We next examined whether lysolecithin, a constituent of modified lipoproteins, affects endothelial heparan sulfate proteoglycan (HSPG) production and monocyte binding. Lysolecithin (10–200 μM) decreased total 35SO4 in SEM (20–75%). 2-fold more monocytes bound to SEM from lysolecithin-treated cells than to control SEM. Heparinase treatment did not further increase monocyte binding to lysolecithin-treated SEM. HSPG degrading activity was found in medium from lysolecithin-treated but not control cells. 35SO4-labeled products obtained from labeled matrix treated with lysolecithin-conditioned medium were similar in size to those generated by heparinase. These data suggest that lysolecithin-treated endothelial cells secrete a heparanase-like activity. We hypothesize that decreased vessel wall HSPG, as occurs in atherogenic conditions, allows increased monocyte retention within the vessel and is due to the actions of an endothelial heparanase.

One characteristic of the atherosclerotic lesion is the presence of lipid-rich macrophages termed foam cells. Many of these cells are descendants of blood monocytes that have accumulated within the subendothelial space and, in this location, have ingested lipoprotein lipid (1). In animal models, elevated amounts of circulating lipoproteins can lead to migration of these cells are descendants of blood monocytes that have accumulated within the subendothelial space and, in this location, have ingested lipoprotein lipid (1). In animal models, elevated amounts of circulating lipoproteins can lead to migration of monocytes and macrophages (2). Monocytes may adhere to SEM adhesion proteins, such as collagen, fibronectin (FN), laminin, and vitronectin (8). These proteins contain domains (such as Arg-Gly-Asp) that can interact with monocyte cell surface integrins (9). Among these protein-protein interactions, the ones between monocyte VLA-4 and FN and between monocyte MAC-1 and fibrinogen have been postulated to be of particular importance (10).

Apart from the adhesion proteins, a significant proportion of the SEM is composed of proteoglycans (PG), negatively charged polysaccharides that play an important role in several cellular processes (11–13). Each proteoglycan molecule contains glycosaminoglycan (GAG) carbohydrate chains and a core protein. Although SEM PG contain three classes of GAG (heparan sulfate, chondroitin sulfate, and dermatan sulfate), heparan sulfate is by far the most abundant, and HSPG accounts for about 80% of SEM PG produced by cultured EC (14). Three species of HSPG were identified in cultured bovine aortic EC, one of which, perlecain, has a core protein size of 400 kDa and is associated with basement membrane (15). The composition and content of vessel wall PG change during development of the atherosclerotic lesion (16–20). Arterial wall dermal sulfate and chondroitin sulfate content increase during atherogenesis; dermal sulfate and chondroitin sulfate have been postulated to retain LDL within the vessel wall (21). In contrast, there is a decrease in HSPG in atherosclerotic vessels (19, 20). The significance of this decrease in HSPG has not been addressed.

The present investigation was undertaken to understand the significance and the biochemical mechanisms of these alterations in SEM PG. The specific questions we asked were whether a decrease in HSPG facilitates monocyte binding to SEM and whether the HSPG levels are altered when EC are exposed to lipoproteins and atherogenic lipids such as lysolecithin. Lysolecithin is a component of atherogenic lipoproteins such as oxidized LDL and β-migrating very low density lipoprotein and has been postulated to be an important causal agent of atherosclerosis (22). Our results provide initial evidence that

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† The abbreviations used are: EC, endothelial cell(s); HSPG, heparan sulfate proteoglycan(s); SEM, subendothelial matrix; FN, fibronectin; LDL, low density lipoprotein(s); ECCM, endothelial cell conditioned medium; BSA, bovine serum albumin; PG, proteoglycan(s); GAG, glycosaminoglycan(s); DMEM, Dulbecco’s modified Eagle’s medium; FBS, fetal bovine serum; DMEM-BSA, DMEM containing 3% BSA; lysolecithin-induced alteration of subendothelial heparan sulfate proteoglycan increases monocyte binding to matrix.
SEM HSPG play an important role in preventing monocyte binding to SEM and that their levels are altered in response to specific stimuli. Furthermore, we show that decreases in SEM HSPG with lyssolecithin are associated with the production of a heparanase-like activity by EC.

**EXPERIMENTAL PROCEDURES**

**Materials**

- L-α-Lyso phosphatidylcholine (lyssolecithin, cat. no. L 1381) from bovine brain was purchased from Sigma. L-[4,5-3H]Leucine (147 Ci/mmol) and [35S]sulfate aqueous solutions were obtained from Amersham Corp.
- Heparinase and heparitinase were purchased from either Sigma or Sekagaku America Inc. (Bethesda, MD). Chondroitin ABC lyase was from Sekagaku America Inc. 1 unit will form 0.1 μmol of unsaturated uronic acid/h.
- l-lactate dehydrogenase (LDH; Sigma) was used as a nonspecific marker of monocyte viability.

**Cells**

Monocytes—THP-1 cells were purchased from the American Type Culture Collection (Rockville, MD) and grown in RPMI 1640 medium (Life Technologies, Inc.) containing 10% fetal bovine serum (Gemini Bioproducts Inc., Calabasas, CA).

- Endothelial Cells—Bovine aortic EC were isolated and cultured as described (23). The cells (10–15 passages) were grown in Dulbecco’s modified Eagle’s medium (DMEM) containing 10% fetal bovine serum (FBS) (Life Technologies, Inc.). Subendothelial Matrix—Confluent EC monolayers were grown in 24- or 48-well culture dishes (Falcon, Becton Dickinson, Lincoln Park, NJ). SEM was prepared as described previously (24). EC monolayers were washed three times with phosphate-buffered saline and incubated for 5 min in a solution containing 20 mM NH₄OH and 0.1% Triton X-100 at room temperature. Detached cells were removed by washing three times with phosphate-buffered saline followed by three times with DMEM containing 3% bovine serum albumin (DMEM-BSA).

**Monocyte Binding**

Monocytes were incubated with DMEM-BSA lacking leucine for 30 min prior to labeling. Approximately 100 μCi of [3H]leucine was added to 1 × 10⁶ cells and incubated for another 2 h under cell culture conditions. Labeled cells were centrifuged at 800 rpm for 5 min to remove the label. The cells were then washed four times with DMEM-BSA and suspended in DMEM-BSA. Suspended cells were then added to either monolayers of EC or SEM in 48-well plates (2–4 × 10⁵ cells/well). Binding was continued for 1 h at 37°C. The spontaneous release of radioactivity under these conditions was about 5%. Unbound monocytes were removed by washing four times with DMEM-BSA and suspended in DMEM-BSA. Suspended cells were then added to either monolayers of EC or SEM in 48-well plates (2–4 × 10⁵ cells/well). Binding was continued for 1 h at 37°C. The spontaneous release of radioactivity under these conditions was about 5%. Unbound monocytes were removed by washing four times with DMEM-BSA, and bound radioactivity was extracted by incubating in 0.1 N NaOH containing 0.1% SDS for 30 min at 37°C and counted. The number of monocytes bound to endothelial monolayer (approximately 30% of cells added) was about 2–3-fold more than that bound to SEM. In some experiments monocyte binding was carried out in DMEM containing 10% calf serum. For enzyme treatments, EC monolayers or SEM were incubated for 1 h at 37°C with different concentrations of heparinase/heparitinase or chondroitinase and washed, and then monocytes were added. To test the effect of lyssolecithin, EC were incubated with 50 μM lyssolecithin (from a 10 mM stock solution in 100% ethanol) for 16 h under cell culture conditions. Control cells received an equal amount of ethanol. SEM was prepared from control and lyssolecithin-treated cells as described above.

**Metabolic Labeling**

EC were labeled with [35S]sulfate for 24–48 h to label cellular PG. Cell-associated PG were assessed by removing cells with NH₄OH/Triton X-100 as described above. SEM PG were extracted either by incubation with 0.1 N NaOH/SDS or with 6 M guanidine hydrochloride for 1 h. Alternatively, SEM were incubated with heparitinase, and released radioactivity was measured to assess heparan sulfate. Total EC proteins were labeled by incubating cells with [3H]leucine for 2 h at 37°C. Unincorporated amino acid was removed, and total protein synthesis was assessed either by extraction of cells with NaOH/SDS or by precipitation with 10% trichloroacetic acid.

**Measurement of HSPG Degrading Activity of EC**

Confluent monolayers of EC in T-175 culture flasks were incubated for 16 h in DMEM with 10% FBS with or without 50 μM lyssolecithin. Subsequently, ECCM was collected and filtered. EC monolayers and

**RESULTS**

**Effect of Heparinase and Chondroitinase Treatment of EC and SEM on Monocyte Binding**—To examine whether removal of HSPG from EC or from SEM affects monocyte binding, the number of monocytes binding to control and heparinase-treated EC and SEM was studied. Treatment of EC with 1 unit of heparinase did not significantly change the amount of THP-1 monocytes bound to EC (Fig. 1). In control experiments, heparinase at this concentration decreased 125I-lipase binding to EC by >60% (23). In some experiments, a small, <20% decrease in the number of monocytes adherent to EC was found with chondroitinase treatment.

The effect of similar treatments on monocyte binding to SEM was then assessed. Treatment of SEM with 1 unit of heparinase increased the number of monocytes bound to SEM to 170% of control (Fig. 1). Chondroitinase treatment of SEM had no effect. Different concentrations of heparinase were then used to treat EC and SEM (Fig. 2). At 3 units/ml concentration, monocyte binding to SEM was increased by 2.2-fold, whereas monocyte binding to EC was not altered. These data suggest that HSPG in SEM inhibit monocyte binding to SEM and that their removal by heparinase increases monocyte binding. In separate experiments treatment of [3H]leucine-labeled SEM with heparinase did not lead to a release of radioactivity, suggesting the absence of proteases in the heparinase preparation (data not shown).

**EFFECTS OF HEPARIN ON MONOCYTE BINDING TO FN**—Endothelial cells produce several matrix adhesion proteins that can poten-
tially play a role in monocyte binding (8). These include collagen type IV, FN, laminin, and vitronectin, all of which contain domains that can bind to GAG. In the following experiment we used FN as a model SEM protein and examined whether the addition of a GAG such as heparin would affect monocyte adherence to FN. Plates were coated with FN (5 μg/ml), and monocyte binding to control plates and BSA- or FN-coated plates was assessed in the presence and the absence of 10 units/ml heparin. FN-coated plates bound 10-fold more monocytes than control or BSA-coated plates (Fig. 3). The number of monocytes bound to the FN-treated plates was decreased by >60% in presence of heparin. Binding to control and BSA-coated plates was not affected by heparin treatment. Furthermore, heparin also inhibited monocyte binding to heparinase-treated SEM by approximately 50% (data not shown). These results suggest that one potential mechanism by which GAG can inhibit monocyte binding to matrix is by interacting with SEM adhesion proteins, e.g. as shown here fibronectin, and interfering with monocyte binding.

Effect of LDL and Lysolecithin on Endothelial HSPG Metabolism—Atherosclerotic vessels have altered proteoglycan levels (16–19) and some in vitro studies have shown that LDL affect cellular PG metabolism (26, 27). We therefore tested whether LDL or lysolecithin, a component of modified lipoproteins, alters EC PG metabolism. PG production was assessed by growing cells in media containing [35S]sulfate. Incubation of EC with LDL (500 μg/ml) or lysolecithin (50 μM) had no significant effect on the amount of cell-associated PG (Fig. 4A). Similarly, LDL had no significant effect on the amount of [35SO4] incorporatd into SEM PG. In contrast, lyssolecithin decreased SEM PG by 55% (Fig. 4B); heparinase-releasable PG (HSPG) decreased by 60% (Fig. 4B, inset). These data demonstrate that lyssolecithin primarily decreased the amount of HSPG. At 25–200 μM concentration, lyssolecithin decreased SEM PG by 25–70% (Fig. 4C). Direct analysis by SDS-polyacrylamide gel electrophoresis and autoradiography of [35SO4]-labeled SEM proteins revealed decreased [35SO4] incorporation into a large (>500 kDa) proteoglycan in lyssolecithin-treated cells (Fig. 4D).

To determine whether the lyssolecithin altered cellular metabolism, e.g. by causing cell toxicity, total protein synthesis was assessed. [3H]leucine incorporation into cellular proteins was not affected by lyssolecithin treatment.

Lyssolecithin Increases Monocyte Binding to SEM—Because lyssolecithin decreased the amount of [35SO4] incorporated into SEM PG, we next tested whether lyssolecithin treatment altered monocyte binding to SEM. Exposure of EC to lyssolecithin (50 μM) increased monocyte adhesion to EC by approximately 2-fold, in agreement with published studies (28). In addition, lyssolecithin treatment increased the number of monocytes adhering to SEM by 1.8-fold (Fig. 5). Treatment of EC with LDL had no significant effect on the binding of monocytes either to EC (not shown) or SEM (Fig. 5).

To examine whether the increased monocyte binding to SEM in lyssolecithin-treated cells was due to a decrease in the SEM HSPG, we tested whether heparinase would increase monocyte adhesion to SEM from lyssolecithin-treated cells. Heparinase (1 unit/ml) as expected increased monocyte adhesion to control SEM by 65%. In lyssolecithin-treated cells, however, no further increase was observed with heparinase treatment. These data suggest that the lyssolecithin-induced decrease in HSPG resulted in increased monocyte binding, and, for this reason, the increase was not enhanced by heparinase treatment.

EC Secrete a HSPG Degrading Activity in Response to Lyssolecithin Treatment—Decreased SEM HSPG in lyssolecithin-treated cells could result from either 1) degradation of HSPG by the secretion of a protease or a heparanase or 2) decreased synthesis of SEM HSPG. To determine if ECCM from lyssolecithin-treated cells contain HSPG degrading activity, ECCM was prepared from control and lyssolecithin-treated cells as described under “Experimental Procedures” and tested for its ability to release radioactivity from [35SO4]-labeled PG or [3H]leucine-labeled (total proteins) SEM (Fig. 6). Compared with control ECCM, lyso-ECCM released >2-fold more [35S] radioactive activity from SEM. The addition of lyssolecithin to control ECCM did not affect the [35SO4] release. The amount of [35S] radioactive activity released by lyso-ECCM in different experiments varied from 40–60% of the counts released by heparinase treatment (not shown). Lyso-ECCM did not increase the amount of [3H]leucine released. The addition of heparin (100 units/ml) to lyso-ECCM abolished the releasing activity. Similarly, addition of suramin, another heparanase inhibitor, also inhibited the lyso-ECCM activity (not shown). This suggested that the [35S] release was due to heparanase-like activity and not due to the actions of a general protease.

Further experiments were done to confirm the presence of heparanase activity in lyso-ECCM. Several investigators studied the effects of proteases on the large HSPG and showed that the heparan sulfate chains are asymmetrically attached to core protein and treatment with different proteases leads to associ-
ation of [35S]GAG in fragments with molecular masses of 130–200 kDa (29, 30). To determine if lyso-ECCM contained a protease- or heparanase-like activity, SEM was incubated with lyso-ECCM, heparinase (2 unit/ml), trypsin (0.25 mg/ml), or proteinase K (0.5 mg/ml) for 4 h at 37° C. The released [35S] radioactivity (degradation products) was analyzed by size fractionation (25) as described under “Experimental Procedures” (Fig. 7). About 90–95% of the total extractable PG were found to have molecular masses of 100 kDa and did not go through Centricon-100 (Fig. 7, GnHCl bar). Approximately 80–90% of the total radioactivity released by either heparinase or lyso-ECCM passed through a Centricon-100 (molecular weight, <100,000). In contrast only 20–25% of trypsin and proteinase K released radioactivity was filtered. In addition, 45–50% of the heparin-
The present studies were performed to understand the contribution of SEM HSPG to monocyte adhesion. Our data suggest that SEM HSPG functions as a negative regulator of monocyte adhesion to SEM. Removal of SEM HSPG increases monocyte binding by approximately 2-fold. Several matrix proteins have been shown to bind to GAG. This led to the suggestion that cell surface PG play a role in cell-substrate binding (31–34). Sanders and Bernfield (33) showed that mammalian epithelial cells have at least two distinct cell surface receptors for FN. These cells have a trypsin-resistant molecule that binds to Arg-Gly-Asp sequences and a trypsin labile HSPG that binds to the carboxyl-terminal heparin-binding domain of FN. Other studies have suggested that cell adhesion through PG may be an auxiliary mechanism that complements a more specific integrin-mediated adhesion (35, 36). Several studies have also shown that GAG inhibit integrin-mediated cell binding to FN (35) or to perlec an core protein itself (37).

Vessel wall contains several basement membrane adhesion proteins including collagen, FN, and laminin. Studies have shown that FN is made by aortic cells and rapidly incorporated into extracellular matrix (38). Immunohistochemical studies have also shown that FN is present throughout the vessel wall of normal and atherosclerotic vessels and have suggested that FN may promote monocyte chemotaxis and play a role in the pathogenesis of atherosclerosis (39–41). Hence in our studies we employed FN as a representative of SEM adhesion proteins and as a candidate for monocyte binding. Our results show that GAG inhibit monocyte binding to FN. This inhibition could be due to effects on monocyte integrin-mediated binding or monocyte surface HSPG-mediated binding, both of which are known to be inhibited by GAG. This may also be true for other adhesion proteins present in SEM, such as collagen and laminin, which also contain both GAG and integrin-binding domains. Thus, in the present studies SEM HSPG inhibition of monocyte binding may, in part, be due to HS PG GAG binding to some of these proteins thereby affecting monocyte binding.

Lysolecithin has been implicated in several of the athero-}

genic effects of modified lipoproteins including induction of chemotaxis and expression of EC adhesion proteins (22, 28). Our studies demonstrate another potentially atherogenic action of lysolecithin, increasing monocyte adhesion to SEM. The extent of the observed increase in monocytes adhering to SEM can be explained by the loss of HSPG alone, i.e. the increase in monocyte binding due to lysolecithin treatment was similar to that found after heparanase treatment of SEM from control cells, a 2-fold increase. Moreover, because heparanase treatment of SEM from lysolecithin-treated cells did not lead to a further increase in monocyte adherence, it is likely that the lysolecithin effect is entirely due to the reduction of SEM HSPG.

Heparanase is produced by several mammalian cells including neutrophils, platelets, and tumor cells (42–44). Tumor cell heparanase has been implicated in tumor metastasis (45). Although EC have been postulated to produce heparanase like enzymes in situations such as wound healing and angiogenesis (46), such an activity has not been demonstrated. Matrix-degrading metalloproteases are found in atherosclerotic vessels and are synthesized by lesion macrophages (47, 48), and these enzymes are implicated in extracellular matrix remodeling during atherogenesis. Although such proteases could also alter proteoglycans (49), our data are most consistent with the production of a heparanase-like activity by lysolecithin-stimulated cells. The amount of sulfate-labeled proteins, predominantly PG, were decreased in the SEM but not in cells after lysolecithin treatment. This was associated with the presence in lyso-ECM of an activity that released sulfate but not labeled amino acids from the SEM. Furthermore, this activity was inhibited by heparin, a known heparanase inhibitor, and the 35SO4 degradation products were similar to those released by heparanase. It should be noted that obtaining heparanase in active form in ECCM was not always possible. It is not clear whether the enzyme is rapidly inactivated in the medium or bound to PG and not easily released.

The identity of the endothelial heparanase is not clear. Hoogewerf et al. (25) recently made a very interesting observation that platelet heparanases belong to the CXC chemokine family of peptides that include connective tissue-activating peptide-III and neutrophil-activating peptide-2. These peptides have molecular masses of 8–10 kDa and are different from the platelet heparanase previously characterized (43). These chemokine family of heparanases are also different from those produced by tumor cells (50). Although endothelial cells are not known to produce connective tissue-activating peptide-III and neutrophil activating peptide-2 (51), it is possible that under specific stimulus (e.g. exposure to lysolecithin) endothelial cells may produce these chemokines. In our preliminary experiments using size fractionation of ECCM we were not able to detect the activity in the fraction with a molecular weight of <30,000 (not shown). Experiments to identify whether endothelial heparanase belong to the chemokine family are currently underway.

Exposure of EC to LDL (500 μg/ml) for 24 h neither increased monocyte adhesion to SEM nor changed proteoglycan metabo-
lism. In one previous study, incubation of EC with high concentrations of LDL for 48 h caused a 50% decrease in basement membrane HSPG (52). It is, however, conceivable that the LDL underwent oxidation during the long course of incubation leading to the generation of products such as lyssolecithin. How lyssolecithin perturbs EC is unclear. It should be noted that the effects of lyssolecithin in the present studies were observed in the presence of serum containing media, suggesting that such effects are possible in vivo in the environment of the subendothelial intima. Recent studies have shown that alterations in endothelial function by lyssolecithin are mediated by activation of protein kinase C (53, 54). In addition, lyssolecithin has been shown to inhibit calcium influx in aortic EC (55). We are currently investigating whether similar mechanisms operate with respect to its actions on EC HSPG metabolism.

In summary our studies provide evidence for a protective role for vessel wall HSPG, i.e. preventing monocyte retention in the intima. Based on our data we hypothesize that in normal intima the basement membrane proteins such as FN, laminin, and collagen are masked by HSPG present in SEM. This masking prevents the binding and retention of monocytes within the intima. Our data also suggest an additional atherogenic role for lyssolecithin, i.e. to modulate subendothelial HSPG. Upon exposure to lyssolecithin EC are “activated,” resulting in the secretion of SEM HSPG degrading (heparinase-like) activity. This, we postulate, decreases SEM HSPG and increases monocyte-SEM interaction. In vivo such an effect could increase retention of monocytes within the arterial wall, allowing them to convert into macrophage-rich foam cells. Removal of SEM HSPG, apart from facilitating monocyte retention, may have other atherogenic consequences. It may increase arterial permeability leading to further increase in lipoprotein movement and retention. SEM contains HSPG bound growth factors (56, 57). When released, these factors stimulate smooth muscle cells to migrate and proliferate in the intima. Thus, our results for the first time demonstrate that endothelial cells produce a heparanase activity under specific stimulus, and we postulate that dysregulation of the endothelial heparanase could play an important role in the pathophysiology of atherosclerosis.

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