High-Density Lipoprotein Stimulates Endothelial Cell Movement by a Mechanism Distinct From Basic Fibroblast Growth Factor

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Abstract Endothelial cell (EC) migration is a regulatory event in the formation and repair of blood vessels. Although serum contains substantial promigratory activity, the responsible components and especially the role of lipoproteins have not been determined. We examined the effect of plasma high-density lipoprotein (HDL) on the movement of ECs in vitro. Confluent cultures of bovine aortic ECs in serum-free medium were "wounded," and migration was measured after 24 hours. HDL-stimulated migration in a concentration-dependent manner with a half-maximal response at 26–40 μg cholesterol per milliliter and a maximal twofold stimulation at ≥150 μg cholesterol per milliliter. HDL-stimulated migration was not due to cell proliferation, since migration was increased in the presence of hydroxyurea at a concentration that blocked proliferation. At optimal concentrations, HDL was at least as stimulatory as basic fibroblast growth factor (FGF). However, the activity of HDL was not due to contamination by basic FGF, since antibodies to basic FGF did not block HDL-stimulated movement and since the maximum promigratory activities of basic FGF and HDL were additive. These results indicate that HDL and basic FGF may use distinct signaling pathways to initiate EC movement. This possibility was confirmed by results showing that pertussis toxin suppressed basic FGF-stimulated but not HDL-stimulated EC motility and that inhibitors of phospholipase A2, arachidonic acid and ONO-RS-082, also blocked the promigratory activity of basic FGF but had no effect on the activity of HDL. The promigratory activity of HDL may accelerate the regeneration of the endothelium after a denuding injury in vivo and suggests a new mechanism by which HDL may be protective against cardiovascular disease. (Circ. Res. 1994;74:1149-1156.)

Key Words • basic fibroblast growth factor • cell motility • endothelial cells • high-density lipoprotein • wound healing

Migration and proliferation of vascular endothelial cells (ECs) are initiating events in the formation of capillaries during normal development and tumor angiogenesis. In addition, a continuous and intact monolayer of ECs is required for the maintenance of normal vessel wall properties, including impermeability and nonthrombogenicity. However, the integrity of the endothelium may be transiently or chronically disrupted by EC turnover, traumatic injury after balloon angioplasty, vascular grafting, organ implantation, or other pathological damage. Rapid regeneration of the endothelium under these circumstances is a critical process in the response to the injury. It is believed that migration is the rate-limiting process in the repair of endothelium, since it is an early event that is followed by proliferation. In fact, increased proliferation may be due to the release from contact inhibition caused by cell migration.

A number of agents are known to regulate EC movement in vitro, including vascular permeability factor, scatter factor, and basic fibroblast growth factor (FGF). Among these, basic FGF is believed to play a physiological role, since ECs themselves contain and release the factor and since antibodies to basic FGF substantially block migration in vitro, suggesting that endogenous basic FGF is responsible for basal EC motility. Both basic and acidic FGFs accelerate reendothelialization of denuded blood vessels after balloon catheterization in vivo. The signaling pathways that regulate basic FGF-stimulated EC migration are less well understood than those involved in proliferation. Activation of FGF-receptor tyrosine kinase activity is an early event in the mitogenic response of cells to basic FGF, but its role in migration is not clear. Among the FGF-stimulated processes that may be involved in EC movement are transient gene expression, production of plasminogen activator and metalloproteinases, modulation of synthesis of extracellular matrix components, and cytoskeletal reorganization (see Reference 13 for review).

Migration of ECs and other cells is markedly stimulated by serum. Whole blood serum contains more EC promigratory activity than plasma-derived serum, suggesting that platelet factors may be involved, but this result is controversial. Although the role of high-density lipoprotein (HDL) and other lipoproteins on EC movement has not been extensively investigated, several observations suggest that such an activity is plausible. The results of Bürk et al suggest that lipoproteins may regulate 3T3 cell migration, since hypercholesterolemic serum has less activity than normal serum. Low-density lipoprotein (LDL) has been shown to increase reendothelialization of wounds in vitro, but the stimulation is blocked by x-ray irradiation of the cells, showing that the increase is due strictly to the mitogenic activity of LDL. HDL has also been shown to increase reendothelialization during a 5-day interval after wounding, but the roles of cell prolifera-
tion and migration have not been distinguished. In view of the known mitogenic activity of HDL, this distinction is critical. In our previous studies, we have shown that oxidized LDL is a potent inhibitor of EC migration in vitro, whereas unmodified LDL is somewhat stimulatory. Given these studies, the continuous interaction of EC with plasma lipoproteins in vivo, and the known inverse correlation of HDL with coronary heart disease, we have examined in the present study the effects of HDL on EC motility and compared its mechanisms of action with basic FGF, the prototypical agonist of EC movement.

Materials and Methods

Cell Culture and Media

ECs were isolated from adult bovine aortas essentially as described. They were subcultured by trypsinization and grown to confluence in Dulbecco’s modified Eagle medium and Ham F-12 medium (GIBCO-BRL) containing 5% fetal bovine serum (HyClone Laboratories). The identity of the cells was confirmed by their nonoverlapping cobblestone morphology and by factor VIII-related antigen immunofluorescence. All EC incubations were at 37°C in a humidified atmosphere of air containing 5% CO2. For migration studies, the cells were grown to confluence in serum-containing medium in 12-well tissue culture clusters (Costar). The cells were made quiescent by changing the medium to serum-free Dulbecco’s modified Eagle medium (Sigma Chemical Co) containing 1 mg/mL gelatin (Sigma) for at least 24 hours before use. Cell proliferation was measured as incorporation of [3H]thymidine (73 Ci/mmol, DuPont NEN) into labeled nuclei detected by autoradiography. Cellular protein synthesis was measured as incorporation of [116 Cl/mmol, DuPont NEN] into a cell monolayer fixed with trichloroacetic acid.

Measurement of EC Migration

EC migration was measured by the razor-wound method essentially as described earlier. Confluent and quiescent EC cultures were wounded with a razor pressed gently through the cell layer into the plastic well to mark the origin and drawn through the monolayer to remove cells on one side of the wound. The medium was replaced with medium containing 1 mg/mL of gelatin plus lipoproteins or other test materials in a total volume of 0.5 mL. Cell migration was permitted for up to 24 hours and terminated by fixing and staining with Wright-Giemsa stain (modified, Sigma). Migration was quantified by a semiautomated computer-assisted procedure performed by a person blinded with respect to the experimental treatments. A 256-gray level 640×480 pixel image of the cultures was captured by a Sony CCD digital camera mounted on a phase-contrast microscope and was transferred to a Macintosh computer. Image and data analysis were done using the imaging software package provided by Dr Wayne Rasband, National Institutes of Health. In each well, two randomly chosen fields, each consisting of a 1500-µm length of original wound edge, were chosen; the number of cells that crossed the origin line was determined; and the results were summed. The data from duplicate wells were expressed as the mean (±SEM) number of migrating cells per 3000 μm; nearly identical results were found if expressed as the mean distance. All experiments were done two or more times, and representative results are shown.

Preparation of Lipoproteins

Lipoproteins were prepared from freshly drawn citrated normolipemic human plasma to which EDTA was added before ultracentrifugation. LDLs (density, 1.019 to 1.063 g/mL) and HDLs (density, 1.063 to 1.210 g/mL) were isolated by sequential ultracentrifugation. Some preparations of HDL were further purified by a second ultracentrifugation at the higher density limit; these lipoproteins yielded results that were essentially identical to those obtained without the additional step. The homogeneity of lipoproteins was verified by the appearance of a single band after agarose electrophoresis and staining with Coomassie blue and oil red O. All lipoproteins were sterilized by passage through a 0.22-µm filter (Millipore) before use, and protein concentration, total cholesterol (Boehringer Mannheim), and endotoxin (Pierce Chemical) were determined for all preparations. Lipoprotein oxidation was minimized by the addition of 0.3 mmol/L EDTA to all preparative solutions; the thiorbarbituric acid reactivity of lipoproteins was low, generally <0.09 and 0.03 nmol malondialdehyde per milligram cholesterol for HDL and LDL, respectively. Lipoprotein-deficient serum (LPDS) was prepared by adjusting the density of the serum to 1.25 g/mL, followed by ultracentrifugation.

Other Materials

Human recombinant basic and acidic FGF and a neutralizing monoclonal anti-basic FGF antibody were from Upstate Biotechnology. Pertussis toxin, aristolochic acid, and ONO-RS-082 were from Biomol, and all other reagents were from Sigma.

Results

We first compared the promigratory effect of serum with that of LPDS to determine the total contribution of lipoproteins. Serum at an optimal concentration stimulated EC migration up to 80% more than the control value, but LPDS had only half the maximum activity of serum, suggesting that a promigratory agent in serum was absent in LPDS (Fig 1). To determine the relative promigratory activities of LDL and HDL, LPDS at a maximal stimulatory concentration was supplemented with both lipoproteins at concentrations proportional to their plasma abundance. Both HDL and LDL increased the promigratory activity of LPDS (Fig 2). HDL was significantly more potent than LDL, and at a level equivalent to that in 7.5% serum, it almost completely restored EC motility to the level stimulated by whole serum. However, the difference in activity between 2.5% serum and lipoprotein-deficient serum was not completely accounted for by the activity of HDL at 2.5% serum equivalents, and it is possible that some
FIG 2. Bar graph comparing the relative promigratory activities of high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Wounded endothelial cell (EC) cultures were incubated with 2.5% lipoprotein-deficient serum (LPDS, open bar), 2.5% serum (black bar), or 2.5% LPDS in the presence of 2.5%, 7.5%, or 25% of the serum-equivalent of HDL (dark striped bars) or LDL (light striped bars). EC migration was measured after 22 hours; migration of serum-free untreated cells was 269±8 cells per 3000 μm.

activity of either HDL was lost during preparation or that other lipoprotein fractions might account for the remaining activity.

The promigratory activity of HDL by itself was examined in serum-free medium and compared with an optimal concentration of basic FGF. Phase-contrast microscopy showed that the stimulation by HDL was concentration dependent, with a maximum stimulation comparable to that of basic FGF at 10 ng/mL (Fig 3). Quantification of these results (Fig 4A) showed that the maximum stimulation by HDL was ≈80% at 150 μg cholesterol per milliliter (or 600 μg protein per milliliter, expressed for comparison with other proteins), with a half-maximum activity at ≈25 μg cholesterol per milliliter (100 μg protein per milliliter). There was an apparent morphological difference between HDL-stimulated and basic FGF–stimulated ECs: the former maintained the polygonal appearance of cells in a confluent monolayer, whereas the latter were distinctly elongated (Fig 3 and data not shown). In many repeti-

FIG 3. Photomicrographs showing the effect of high-density lipoprotein (HDL) and basic fibroblast growth factor (bFGF) on wound-induced migration of endothelial cells. Wounded endothelial cell cultures were incubated for 22 hours with HDL or bFGF in serum-free medium at the concentrations indicated. The cells were fixed and stained with Wright-Giemsa and visualized by phase-contrast microscopy.

FIG 4. Graphs showing the effect of high-density lipoprotein (HDL) and basic fibroblast growth factor (FGF) on wound-induced migration of endothelial cells. A, Wounded endothelial cell cultures were incubated with HDL (●) or bovine serum albumin (BSA, □), and cell migration was determined after 22 hours. Migration of unstimulated endothelial cells was 304±34 per 3000 μm. B, Conditions were the same as in panel A, but cells were incubated with basic FGF (●) or acidic FGF (○). Migration of unstimulated endothelial cells was 222±10 cells per 3000 μm.

tions of this experiment, with at least eight different HDL preparations, a maximum stimulation of 40% to 100% was observed with a half-maximum concentration between 25 and 40 μg cholesterol per milliliter. Nearly identical results were seen with several distinct isolates of bovine aortic ECs between passages 6 and 19. Bovine serum albumin at a protein concentration comparable to HDL did not significantly stimulate EC movement, indicating that the effect of HDL was specific and not just a result of additional protein (Fig 4A). The latter possibility was also made less likely in view of the presence of 1 mg/mL gelatin during all experiments. The maximal stimulation was comparable to the 75% stimulation by basic FGF at 10 ng/mL (Fig 4B), an increase consistent with previous reports. Acidic FGF was considerably less effective, with a maximal stimulation of only 30% at 50 ng/mL; the comparatively low activity of acidic FGF may be due to the absence of the synergistic agent heparin.

To determine the time required for HDL to stimulate EC movement, a time course was examined during a 24-hour period. The amount of migration increased
almost linearly during this period, with the HDL-treated cells showing a higher migration rate than untreated cells as early as 3 hours, the minimum interval required to accurately measure migration by this method (Fig 5). Time-lapse videomicrography showed that cell movement was clearly visible as early as 1 hour after treatment with HDL and basic FGF but not detectable until 2 to 3 hours in untreated cells (data not shown). When HDL was removed 1 hour (or 4 hours, data not shown) after the injury was made, there was little stimulation of movement, indicating that HDL was continuously required (Fig 6); a similar requirement was observed for basic FGF. This result showed, in addition, that the stimulation by HDL was not due to a coating of the plastic surface after the injury was made, suggesting that an interaction with the cells themselves may be responsible for its activity.

Since HDL is a known mitogen for ECs and other cells,18,19 we considered the possibility that cell proliferation, in addition to migration, contributed to the appearance of cells in the wound region. To differentiate these activities of HDL, EC migration was measured in the presence of hydroxyurea, an inhibitor of the G1/S-phase transition of the cell cycle. Phase-contrast photomicrography clearly showed that the stimulation of EC migration by HDL was not at all diminished by hydroxyurea (Table); basal (unstimulated) and basic FGF–stimulated migration was also unaffected by hydroxyurea. HDL (and basic FGF) increased the migration of ECs by >50% whether or not they were treated with hydroxyurea (which had little effect by itself). To show that hydroxyurea effectively blocked EC proliferation, the cells were incubated with [3H]thymidine, and labeled nuclei were identified by autoradiography. The Table shows that cell division was completely blocked by 1 mmol/L hydroxyurea. These data also confirm the mitogenic activity of HDLs (and basic FGF) observed by others, even in the absence of serum factors. Interestingly, in all treatments the cells behind the cutting edge were much less actively proliferative than the migrating cells. It is possible, if not likely, that these processes are related and that cell migration leads to increased proliferation by decreasing contact inhibition or by decreasing the cell’s requirements for growth stimulators.4,5

Multiple peptide growth factors, and possibly basic FGF,28 are present in serum and may be associated with HDL. To test whether HDL-bound basic FGF was responsible for the activity of HDL, we examined the ability of a neutralizing antibody to basic FGF to block HDL-stimulated migration. An antibody to human basic FGF inhibited 52% of basic FGF-stimulated EC migration (Fig 7). In contrast, the inhibition of the activity of HDL was much less (28%) and consistent in magnitude with the decrease in migration due to inactivation of cell-derived basic FGF. This result suggested that the active agent in HDL was not basic FGF but did not eliminate the possibility that HDL and basic FGF shared similar promigratory signaling pathways. To test this possibility, the effect of basic FGF (at an optimal stimulatory concentration of 10 ng/mL) on HDL-stimulated movement was examined. The maximum stimulation by basic FGF alone was ≈65%, and that of HDL alone was ≈80% (Fig 8). Addition of basic FGF increased the stimulatory activity by 60% to 80% at all concentrations of HDL, with a maximum stimulation of 150%, higher than that observed by us under any other conditions. These data indicate that HDL and basic FGF stimulate EC migration by distinct mechanisms, and furthermore, if the promigratory agent in HDL is a peptide growth factor, then it follows a pathway distinct from basic FGF.

To distinguish between the promigratory mechanisms of basic FGF and HDL, specific inhibitors of signal transduction pathways were investigated. We recently found that pertussis toxin, a factor that ADP-ribosylates and inactivates susceptible G-like G proteins,28 blocked EC movement in response to basic FGF but not to serum.29 In agreement with those results, Fig 9 shows that basic FGF–stimulated movement was markedly suppressed by pertussis toxin (77% inhibition). Pertussis toxin also blocked “unstimulated” EC motility by 64%), consistent with the role of endogenous basic FGF in this process.3 In contrast, EC motility stimulated by HDL, as well as by serum, was only marginally inhibited by the toxin (18% and 14%, respectively). These data indicate that HDL may be the serum component responsible for pertussis toxin–insensitive serum-stimu-
Effect of Hydroxyurea on High-Density Lipoprotein– and Basic Fibroblast Growth Factor–Stimulated Endothelial Cell Migration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EC Migration, No. of Cells</th>
<th>EC Proliferation, No. of Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>305±15</td>
<td>91±6</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>340±5</td>
<td>0±0</td>
</tr>
<tr>
<td>HDL</td>
<td>480±26</td>
<td>242±13</td>
</tr>
<tr>
<td>HDL+hydroxyurea</td>
<td>473±1</td>
<td>0±0</td>
</tr>
<tr>
<td>Basic FGF</td>
<td>470±2</td>
<td>231±12</td>
</tr>
<tr>
<td>Basic FGF+hydroxyurea</td>
<td>464±13</td>
<td>0±0</td>
</tr>
</tbody>
</table>

EC indicates endothelial cell; HDL, high-density lipoprotein; and FGF, fibroblast growth factor. The results are expressed as mean±SEM for the number of migrating or proliferating cells per 3000 μm.

Wounded EC cultures were treated with HDL (100 μg cholesterol per milliliter) or basic FGF (10 ng/mL) in serum-free medium containing [3H]thymidine (1 μCi/mL) and in the presence or absence of hydroxyurea (1 mmol/L). After 22 hours, the medium was aspirated, and the cells were washed with phosphate-buffered saline, fixed with methanol, and stained with hematoxylin. The [3H]thymidine-labeled nuclei of proliferating cells were identified by autoradiography after coating the cultures with photographic emulsion. Proliferating cells in only the wound region were counted.

The results demonstrate that basic FGF and HDL stimulate movement by different pathways, with only the former requiring the activity of pertussis toxin–sensitive G proteins.

Basic FGF–mediated EC movement requires the release of arachidonic acid by G protein–mediated activation of phospholipase A2. To test whether HDL-stimulated migration likewise requires mobilization of arachidonic acid (albeit by a pertussis toxin–insensitive pathway), the effects of specific inhibitors of phospholipase A2 were determined. Aristolochic acid and ONO-082 blocked basic FGF–stimulated EC migration by up to 85% (Fig 10); the concentrations at which these inhibitors blocked basic FGF–stimulated movement corresponded to the concentrations reported for their specific inhibition of phospholipase A2. In contrast, ONO-082 had no effect on HDL-stimulated cell movement, and aristolochic acid had only a moderate suppressive activity. Measurement of protein synthesis using [3H]leucine showed that the inhibition of migration by the inhibitors was not due to cytotoxicity, since aristolochic acid did not inhibit the rate of protein synthesis, and the inhibition by ONO-082 was small (and only at the highest concentration). These data show that HDL-stimulated EC movement, unlike FGF-stimulated movement, does not require phospholipase A2 activity.

Discussion

The experiments described in the present study demonstrate that HDL is a potent promigratory agent that stimulates the movement of EC up to twofold at concentrations below the normal physiological range of 250 to 500 μg HDL cholesterol per milliliter. The stimulation is specific, since other serum proteins, eg, albumin, are without activity, and the magnitude of the stimulation is comparable to that of basic FGF, the prototypical...
agonist of EC movement. These results represent, to our knowledge, the first report of stimulation of cell movement by normal lipoproteins (with the exception of our previous studies of oxidized LDL, which showed that native LDL was mildly promigratory). Monocyte chemotaxis induced by the EC product, monocyte chemotactic protein-1, has been shown to be stimulated by oxidized LDL. Similarly, other laboratories have shown that specific modified lipoproteins, including oxidized LDL and acetoacetylated LDL but not native LDL, induce chemotactic responses in smooth muscle cells.

Several laboratories have shown that HDL stimulates the proliferation of ECs and other cells. The increased movement of cells in response to HDL was observed as early as 1 hour by videomicrography, thus suggesting that the migratory response was an early event that was independent of, or at least preceded, proliferation. To minimize the fraction of cells dividing, the migration period was generally limited to 22 hours; nevertheless, a significant number of migrating cells were observed to go through S phase (Table). To demonstrate that the increased number of cells in the wound in HDL-treated cultures was due to cells moving into the wound rather than division of cells already in the wound, the latter process was specifically blocked by hydroxyurea. The results clearly show that movement of ECs into the wound does not require proliferation and that HDL can act as a promigratory agent independent of its action as a growth promoter. The ability of hydroxyurea and other agents to block cell proliferation, but not migration, has been well documented and used as evidence of the independence of migration and proliferation. In contrast, the high fraction of rapidly migrating cells in the wound area that incorporate [3H]thymidine, compared with the more slowly moving cells behind the wound edge, suggests that migration and replication may be related, as has been observed previously.

When HDL remained on the EC cultures only long enough to coat the plastic dish, the rate of cell movement was essentially identical to that of unstimulated cells. This result suggests that HDL does not function as a matrixlike attachment or spreading factor but that a direct interaction of HDL with the cells may be required for promigratory activity. One possibility is that HDL stimulates a specific intracellular signaling pathway after binding to a cell surface receptor or after nonreceptor-mediated uptake and internalization. High-affinity binding sites for HDLs have been identified on bovine aortic ECs, and a 110-kD protein that binds to HDL and has several receptor-like features has been cloned and expressed. Binding of HDLs to ECs may be facilitated by apolipoprotein AI and apolipoprotein AII, which share a common receptor. An alternate uptake mechanism has been advanced in which HDLs bind to ECs primarily through lipid-lipid interactions rather than a specific polypeptide receptor. HDL may also exert its promigratory activity without directly interacting with cells. As one possibility, HDL, acting as a "lipid sink," may remove from the cells an endogenous antimigratory molecule. Although we have no direct evidence for this mechanism, the interaction of lipids with HDL apolipoproteins and with native HDL has been long appreciated, and our own results suggest that specific oxidized lipids have substantial antimigratory activity.

We do not yet know the molecular mechanisms underlying the promigratory activity of HDL. We have shown that an antibody to basic FGF does not block the activity of HDL, showing that the active agent in HDL activity is not basic FGF. In agreement with this result, the promigratory activities of HDL and basic FGF have been found to be completely additive, indicating that they involve different mechanisms. A similar additive relation has been reported by others for the mitogenic activities of the two factors. The rapid induction of migration by HDL is consistent with a signal transduction mechanism. The signaling pathways used by HDL are not well understood (see Reference 43 for review), but others have reported a role for G protein–coupled pathways in the stimulation by HDL of muscarinic receptors in chick heart cells and a pertussis toxin–sensitive activation of phospholipase C in platelets.
Our experiments indicate that the stimulation of EC movement by HDL, unlike basic FGF, does not require a pertussis toxin–sensitive G protein. We have recently shown that the stimulation of movement by basic FGF requires G protein–mediated release of arachidonic acid. This finding is consistent with evidence showing that arachidonic acid release is an early response of ECs to basic FGF and that activation of phospholipase $A_2$ by multiple agonists may be coupled to pertussis toxin–sensitive G proteins. Our results with two specific inhibitors of phospholipase $A_2$ show that this enzyme is not required for HDL–stimulated EC motility and are further evidence for the differential utilization of signaling pathways by HDL and basic FGF. HDL has also been shown to stimulate phosphorylation of 27-kD proteins, to block G protein interaction with its receptor, to induce a transient release of $Ca^{2+}$, and to activate protein kinase C. The role that these and other intracellular signaling pathways play in HDL–mediated migration is not known. The effect of HDL on other processes required for EC migration such as cytoskeletal rearrangement and secretion of matrix-degrading proteases is likewise unknown.

Epidemiologic and clinical studies have shown that plasma HDL levels are inversely related to the incidence of coronary artery disease. Recent studies with transgenic animals suggest that the apolipoprotein $A_1$ component of HDL may be protective against atherosclerosis. Several mechanisms have been suggested for the putative antiatherogenic activity of HDL. One suggested mechanism is the transfer of excess cholesterol from peripheral tissues to the liver. According to a second proposed mechanism, HDL prevents the oxidation of LDL and suppresses several of the potentially damaging activities of oxidized LDL, including toxicity to vascular cells and stimulation of monocyte transmigration across the endothelium.

Our own results on EC movement invite speculation on an additional mechanism by which HDL may resist the initiation of atherosclerosis. Studies in animal models have shown that deendothelialization of the rat aorta with a balloon catheter is followed by a reproducible series of events, beginning with rapid platelet aggregation, followed by slow reendothelialization, and culminating in marked intimal thickening due to SMC migration and proliferation that is apparent within weeks. A correlation between the duration of endothelial denudation and the degree of intimal thickening has been demonstrated; in fact, injured regions that are covered by regenerated endothelium within 1 week after injury are completely spared. We suggest that high plasma levels of HDL may stimulate the migration (and subsequent proliferation) of ECs into a wound region, thus reducing the duration of exposure of a wound to bloodborne elements. This process could be involved in the rate of recovery of the endothelium during normal vessel wall processes, such as denuding endothelial injury, or after clinical procedures, including percutaneous transluminal angioplasty, vascular reconstruction, or organ transplantation.

Acknowledgments

This work was supported by grants HL-40352 and HL-41178 from the National Heart, Lung, and Blood Institute, National Institutes of Health. Dr Fox is an Established Investigator of the American Heart Association. Dr Sa is a Fellow of the American Heart Association, Northeast Ohio Affiliate, Inc. We thank Richard F. Marquardt for assistance with the image and data analysis and James Lang for photography.

References


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High-density lipoprotein stimulates endothelial cell movement by a mechanism distinct from basic fibroblast growth factor.
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Circ Res. 1994;74:1149-1156
doi: 10.1161/01.RES.74.6.1149

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