Low Density Lipoproteins Interact With Acidic Fibroblast Growth Factor and Modify Its Function

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Objective—Oxidized LDL (oxLDL) was shown to trigger the release of acidic fibroblast growth factor (FGF-1). Because these components are likely to be present simultaneously in the atherosclerotic milieu, we investigated whether oxLDL interacts with FGF-1 and whether this interaction affects FGF-1 functioning.

Methods and Results—Using molecular sieve and electrophoretic mobility shift assays, we found that FGF-1 forms a complex with oxLDL in vitro, in contrast to its low affinity for nonatherogenic, native LDL. The FGF-1/oxLDL complex had a dramatically decreased ability to bind heparin and was nonmitogenic on cultured smooth muscle cells. In human atherosclerotic lesions, the highest FGF-1 immunoreactivity was found in macrophages. With respect to oxLDL accumulation, 2 patterns were distinguished: (1) moderate, intracellular in matrix-rich regions containing viable cells and (2) massive, both cell-associated and extracellular oxLDL deposits in foam cell–rich regions with necrotic areas. The proliferating cell nuclear antigen readings for proliferating cells reflected that the mitogenic activity of FGF-1 was confined to the regions where oxLDL was strictly intracellular and was inhibited in the regions with extracellular oxLDL deposition.

Conclusions—oxLDL, besides being a bulky component of the atherosclerotic lesion, possibly manifests its pathogenicity by complexing FGF-1 and inhibiting its growth-promoting function during atherogenesis. (Arterioscler Thromb Vasc Biol. 2003;23:601-607.)

Key Words: acidic fibroblast growth factor | oxidized LDL | complex formation | proteoglycan | atherogenesis

Atherogenesis is characterized by two major mechanisms: (1) excessive proliferation of a variety of cell types in the arterial intima, which is controlled by growth factors and cytokines, and (2) oxidation and accumulation of LDL in the form of both intracellular and extracellular deposits.1–3 Fibroblast growth factor-1 (FGF-1) is a member of a large family of heparin-binding growth factors. Its role has been established in development and in a variety of pathophysiological situations, including atherosclerosis, through stimulation of angiogenesis and mesenchymal cell proliferation.4,5 Both FGF-1 and FGF receptors (FGFRs) are upregulated in human atherosclerotic lesions.6,7

Local activation of FGF-1 as a mitogen depends on its high affinity to heparin and heparan sulfate proteoglycans (HSPGs), the major components of the vascular extracellular matrix, which are often enriched in atherosclerotic plaques.8 Strong electrostatic interaction of monomeric FGF-1 with heparin provides proper assembly of a dimeric, mitogenically active FGF-1/FGFR complex, which is obligatory for transmembrane signaling via the tyrosine kinase–type receptors.9,10 Binding of FGF-1 to heparin or HSPGs also stabilizes the conformation of FGF-1, thereby protecting it from proteolysis by enzymes present in the extracellular milieu.11

Regarding the lipoprotein aspect of atherogenesis, retention and oxidation of atherogenic LDLs containing apolipoprotein (apo) B are viewed as pathophysiological mechanisms that initiate arterial lesion development involving monocyte chemotaxis, accelerated endocytosis of oxidized LDL (oxLDL) by macrophages, and formation of lipid-laden “foam” cells.1,3 OxLDL induces a number of cytokines and growth factors in vascular cells, exerts mitogenic effects at low concentrations and cytotoxic effects at high concentrations, and are also implicated in the progression of the plaque to vulnerable, highly thrombogenic atheroma.1

Lipoprotein retention in atherosclerosis-prone regions is thought to be caused by the binding of LDLs to proteoglycans (PGs) of the extracellular matrix, which prevents their egress after crossing the endothelial barrier.12 Complexes of apoB-containing lipoproteins with PGs can be produced in vitro and have also been purified from human atherosclerotic lesions.13 The NH2-terminal region of apoB is responsible for lipoprotein association with PGs via ionic interactions between positively charged residues of apoB (lysine and arginine) and negatively charged groups (sulfate and carboxyl groups) of glycosaminoglycan chains of PGs.14,15 Oxidation of LDL increases the net negative charge of LDL particles and...
decreases their binding to PGs, which is thought to switch accumulation of LDL from extracellular to intracellular.16

Thus, in the atherosclerotic milieu, both FGF-1 and lipoproteins interact with HSPGs of the extracellular matrix in the tightly regulated course of their functioning. We reported earlier that oxLDL triggered a massive release of FGF-1 from FGF-1–transfected cells, suggesting that this can be a pathophysiological mechanism of FGF-1 release during progression of atherosclerotic lesions.17 Here, we investigated whether FGF-1 and LDL (native or oxidized), which are likely to be present simultaneously in the extracellular environment of atherosclerotic lesions at certain stages, interact with each other, and whether this interaction alters functioning of FGF-1.

Methods

Materials

Human recombinant truncated FGF-1_{21,154} and full-length FGF-1 (βFGF-1) were provided by Dr W. Burgess (American Red Cross, Rockville, Md). Native LDL and oxLDL were purchased from Intracel and were stored in 0.15 mol/L NaCl–0.01% EDTA–0.1 mmol/L BHT, pH 7.2. Native LDL was isolated by the manufacturer from fresh human plasma by sequential isopycnic ultracentrifugation. Fully oxidized LDL was prepared by dialyzing LDL against CuSO_{4}–containing isotonic saline, pH 7.4. Heparin from porcine intestinal mucosa (average molecular weight, 17 kDa) was from Sigma.

Analysis of FGF-1/Lipoprotein Complex Formation

Molecular Sieve Assay

Samples of recombinant FGF-1_{21,154} (180 ng) were incubated with native LDL or oxLDL (5.0 μg) at a 1:1 protein molar ratio (assuming a molecular weight for FGF-1 of 18 kDa and for apoB100 of 500 kDa18) in 50 mmol/L Tris-HCl, 0.15 mol/L NaCl, pH 7.5, at 37°C for 2 hours. The samples were spun in a centrifuge using Centricon-50 (Amicon) to separate complexed FGF-1 from unbound FGF-1. Retained and pass-through fractions were resolved by SDS–polyacrylamide gel electrophoresis (PAGE; 15% wt/vol acrylamide) under nonreducing conditions followed by Western blot analysis with a mouse monoclonal anti-human FGF-1 antibody (mAb, 1 μg/mL, Sigma) as a primary antibody. Protein bands were visualized with enhanced chemiluminescence reagents (Amersham). Quantitative densitometry was performed with a scanner (Scanjet II CXT, Hewlett-Packard) by measuring the integral densities of experimental and standard bands.17 The integral density of untreated and unfraccionated FGF-1 was considered as 100%.

Gel Mobility Shift Assay

FGF-1_{21,154} samples preincubated with native LDL or oxLDL were resolved in 2% to 16% gradient native PAGE (no β-mercaptoethanol, no SDS) with 90 mmol/L Tris base, 80 mmol/L boric acid, and 3 mmol/L EDTA, pH 8.35, as the electrode buffer.19 Immunoblot analysis was performed with a mouse anti-human FGF-1 mAb or a mouse anti-human apoB mAb (Exocell) as the primary antibody. Nondenatured protein molecular weight markers were from Sigma.

Heparin-Sepharose Affinity Chromatography

FGF-1_{21,154} samples before and after incubation with equimolar protein amounts of native LDL or oxLDL were applied onto a heparin-Sepharose column (HiTrap, Pharmacia LKB Biotechnology) in 50 mmol/L Tris-HCl, pH 7.5. After the unbound proteins were collected with the above buffer, bound proteins were eluted with increasing NaCl concentrations. The elution fractions were analyzed by SDS-PAGE (4% to 20% gradient gels, Bio-Rad) under nonreducing conditions, followed by immunoblot analysis with anti-FGF-1 and anti-apoB antibody.

Solid-Phase Radioimmunoassay

FGF-1 was labeled with Na^{125}I (100 mCi/mL, Amersham Pharmacia Biotech) by using lactoperoxidase beads (Worthington Biochemical Corp).20 Microtiter wells plates (Immulon I, Dynex Technologies) were coated with anti-apoB mAb to immobilize oxLDL. The binding of FGF-1 to oxLDL was performed in the absence or presence of increasing concentrations of cold FGF or heparin. The K_{i} and K_{d} values were obtained by computer analysis of the experimental data with the use of a computer program (LIGAND program21; for details, see http://www.atvb.ahajournals.org).

Assessment of Mitogenic Activity of FGF-1

Primary cultures of mouse aortic smooth muscle cells (SMCs) were isolated from the aortas of BALB/c mice by the explant technique and propagated in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (FBS, Hyclone). Primary cultures of human aortic SMCs (BioWhittaker) were propagated in Smgm-2 BulletKit medium (BioWhittaker) supplemented with 10% FBS.

Cells were plated in 12-well plates at a density of 1 × 10^4 cells/cm², and FGF-1 was added (directly or after preincubation with LDLs; see http://www.atvb.ahajournals.org) at a final concentration of 50 ng/mL in the corresponding low-1% (FBS) serum medium containing 10 U heparin. At indicated time intervals, triplicate wells were trypsinized, and the cells were counted in a Coulter counter.

Immunohistochemistry

Coronary atherectomy specimens were obtained from patients (mean ±SD age, 64 ±11 years) who underwent directional coronary atherectomy at the Washington Hospital Center. Regions of normal media, intimal hyperplasia, myxomatous tissue, inflammation, and neovascularization were identified by using criteria described earlier.22

The atherectomy specimens were stained as described22 with the following primary antibodies: anti-FGF-1 mAb (Sigma), mAb OXL41.1 (Laboratory Vision Corp), anti–proliferating cell nuclear antigen (PCNA, Dako), anti-CD31 (Dako), anti-CD68 (Dako), or anti–α-SM actin (Sigma) mAbs. Components of extracellular matrix were stained by Movat’s pentachrome method.23 (For details, see http://www.atvb.ahajournals.org.)

Results

FGF-1 Forms a Complex With oxLDL

Preliminary indication of interaction between FGF-1 and oxLDL was obtained from filtration of untreated FGF-1_{21,154} or FGF-1_{21,154} after incubation with equimolar protein amounts of native LDL or oxLDL through a Centricron-50 membrane (molecular weight cutoff, 50 kDa). Immunoblot analysis of the retained and pass-through fractions resolved by SDS-PAGE is presented in Figure 1A. For untreated FGF-1, >95% of the protein was detected as an 18-kDa band in the fraction that passed through the molecular sieve (lane 2). In contrast, >97% of FGF-1 preincubated with oxLDL was found in the retained fraction (lane 5), indicating formation of a complex. Because FGF-1 in lane 5 in the presence of SDS was detected mainly as an 18-kDa band, interaction between FGF-1 and oxLDL is likely noncovalent, ie, either electrostatic or hydrophobic. The retained fraction also contained a minor high-molecular-weight band, resistant to SDS, indicating that complete dissociation of the complex requires a higher SDS concentration. It cannot, however, be ruled out...
that covalent bonds may also be involved, because this band was not detected under reducing conditions (data not shown).

For FGF-1 preincubated with native LDL, 30% to 40% was retained by the sieve, whereas ∼60% to 70% remained unbound (lanes 3 and 4). In contrast to the FGF-1/oxLDL complex, the complex with native LDL was readily dissociable by SDS, indicating weaker interaction. FGF-1 incubated with bovine serum albumin behaved similarly to untreated FGF-1, confirming specificity of the interactions.

Incubation of a constant amount of FGF-1 with increasing amounts of oxLDL revealed that FGF-1/oxLDL binding reaches saturation at 4:1 FGF-1/apoB molar ratio, because at higher ratios FGF-1 was detected in the pass-through fraction. Taking into consideration the average molecular weight of an LDL particle of 2 000 000,18 this implies that approximately 16 FGF-1 molecules can potentially bind 1 oxLDL particle. To avoid dissociation of the complex, FGF-1/lipoprotein interaction was next analyzed by native PAGE without reducing (β-mercaptoethanol) and denaturing (SDS) agents (Figure 1B). Immunoblot analysis with anti–FGF-1 mAb demonstrated that while free FGF-1 migrated toward the bottom of the gel (lane 1), preincubation of FGF-1 with oxLDL led to a drastic shift of its electrophoretic mobility, and FGF-1 was detected as a high-molecular-weight band (lane 3). Testing of the same blot with anti-apoB antibody to detect LDL particles revealed that the positions of FGF-1 and apoB, respectively. Note that localization for FGF-1–positive band (lane 3) coincides with location of apoB-positive band (lane 5). Immunoblot is representative of 3 experiments.

Binding to oxLDL Inhibits FGF-1 Interaction With Heparin

The effect of lipoproteins on the ability of FGF-1 for high-affinity binding to heparin was studied by comparing elution profiles of free FGF-1 and FGF-1 preincubated with equimolar amounts of LDLs (providing a complete complexing of FGF-1 to oxLDL) from a heparin affinity column (Figure 1; see http://www.atvb.ahajournals.org). As expected, FGF-1, which was not exposed to LDLs, manifested a high affinity for heparin and eluted at a high ionic strength (1.5 mol/L NaCl). Preincubation of FGF-1 with oxLDL resulted in a dramatic decrease of its binding to heparin: FGF-1 was already eluted at 0.2 mol/L NaCl and was also present in the unbound fraction (B). Testing of the same blot with anti-apoB antibody to detect the oxLDL particle revealed its presence in the same elution fractions (D), indicating that FGF-1 remained bound to oxLDL.

For FGF-1 preincubated with native LDL, 2 elution peaks were detected—one at a low (0.2 to 0.4 mol/L) and 1 at a high (1.5 mol/L) salt concentration (C). The first FGF-1 peak coincided with the presence of native LDL (E), indicating that this portion of FGF-1 was bound to native LDL. Whereas the first FGF-1 peak constituted ∼30% of total FGF-1, the major portion of FGF-1 remained in a free form and retained a high affinity to heparin (lane C7).

The elution profiles of native LDL and oxLDL presented in Figure 1D and 1E are similar to those reported earlier for native LDL (0.3 to 0.4 mol/L NaCl)14 and consistent with a decreased ability of oxLDL to bind to heparin and HSPGs.16 Thus, FGF-1 complexed to oxLDL loses its heparin-binding ability, suggesting that some residues of FGF-1 that form the heparin-binding site might be involved in complex formation with oxLDL. Alternatively, formation of the oxLDL/FGF-1 complex might perturb the tertiary structure of FGF-1, thus leaving the heparin-binding site inaccessible.

Determination of $K_d$ Value for FGF-1/oxLDL Interaction

To compare affinities of FGF-1 to oxLDL and heparin, we measured $^{125}$I–FGF-1 binding to immobilized oxLDL in the presence of increasing concentrations of cold FGF-1 or heparin (Figure II; see http://www.atvb.ahajournals.org). The $K_d$ value,
characterizing the affinity of FGF-1 for oxLDL, was derived from homologous displacement data and constituted 206 ± 9.7 nmol/L. The $K_v$ value calculated from inhibition of $^{125}$I-FGF-1 binding to oxLDL by heparin was 41 ± 3.5 nmol/L. The latter value is comparable with the $K_v$ for FGF-1/heparin binding reported earlier (35 ± 5 nmol/L). Thus, the affinity of FGF-1 for oxLDL is approximately 5-fold lower than that for heparin.

**Opposite Effects of oxLDL and Native LDL on Mitogenic Activity of FGF-1**

The growth of mouse aortic SMCs in the presence of untreated FGF-1 or FGF-1 preincubated with oxLDL or native LDL is shown in Figure 2A and 2B, respectively. Both truncated FGF-1$_{121-154}$ and full-length FGF-1 were used to test the validity of the results for the in vivo situation. At low serum concentration, mouse SMCs did not proliferate in the absence of FGF-1, whereas addition of FGF-1 markedly stimulated SMC proliferation. Preincubation of FGF-1 with heparin enhanced its mitogenic effect owing to faster assembly of the FGF-1/heparin/FGFR complex, increasing the initial cell number by 1.8-fold at day 5.

Remarkably, preincubation of FGF-1 with equimolar amounts of oxLDL resulted in almost complete inhibition of its mitogenic activity (A, red curve). When a preformed FGF-1/oxLDL complex was subsequently incubated with heparin, the mitogenic activity of FGF-1 was restored only partially (A, green curve), which might reflect partial displacement of oxLDL by heparin because of a higher affinity of the FGF-1/heparin interaction.

Native LDL displayed no inhibitory effect: FGF-1 preincubated with equimolar amounts of native LDL was even more mitogenic than FGF-1 alone and as stimulatory as FGF-1 preincubated with heparin (B, red curve). This phenomenon might be due to a more compact structure acquired by FGF-1 after exposure to native LDL, which facilitates FGF-1 interaction with heparin and FGFR. Indeed, the mitogenic effect was maximally pronounced when FGF-1 was preincubated with native LDL and subsequently with heparin (B, green curve), resulting in a >2-fold increase in cell number at day 5. These mitogenic effects were mediated by FGF-1 but not by LDLs, because neither native LDL nor oxLDL alone affected SMC growth.

To test whether inhibition of mitogenic activity of FGF-1 by oxLDL is a general phenomenon, we extended our study to human aortic SMCs. Preincubation of FGF-1 with oxLDL reduced the end-point cell densities at day 5 by 36 ± 4.3% in comparison with FGF-1 preincubated with heparin. FGF-1 preincubated with oxLDL and subsequently with heparin was 79 ± 3.7% as mitogenic as FGF-1 preincubated with heparin. In contrast, native LDL did not reduce the end-point cell densities, and FGF-1 preincubated with native LDL and subsequently with heparin was 5% to 10% more effective than FGF-1 preincubated with heparin. Thus, oxLDL dramatically inhibited the mitogenic activity of FGF-1 on both mouse and human aortic SMCs, and this inhibition could be only partially reversed by heparin.

**Functional Status of FGF-1 in Human Atherosclerotic Lesions Is Dependent on the Presence of oxLDL in the Extracellular Environment**

To evaluate the physiological relevance of our in vitro findings in human atherosclerotic lesions, we examined 18 coronary atherectomy specimens for distribution of FGF-1 in correlation with the deposition of oxLDL.

The highest immunoreactivity for FGF-1 was found in inflammatory regions, rich in macrophages, lipid-laden foam cells, and giant cells (Figure 3C). The macrophage origin of FGF-1-positive cells was confirmed by their positive staining for a macrophage-specific marker, CD68 (Figure 3D). High FGF-1 immunoreactivity was also found in stellate cells of myxomatous tissue (Figure 3B), previously characterized as a specific phenotype of SMCs. CD31-positive endothelial cells of microvessels were found weakly positive for FGF-1 (Figure 3C, white arrow). Quiescent medial SMCs in normal media (Figure 3A) and spindle-shaped cells in the densely cellular areas of intimal hyperplasia (data not shown) were negative for FGF-1 protein.

Our finding of the highest levels of FGF-1 in macrophages and their derivatives is consistent with earlier reports. Because the FGF-1—expressing macrophage is the major mediator of LDL oxidation and the major accumulator of oxLDL via scavenger receptors in atherosclerotic plaques, our results suggest that interaction between FGF-1 and LDLs, both native and oxidized, is likely to take place in vivo.

Oxidation of native LDL and accumulation of oxLDL accompany progression of atherosclerosis, creating different environment for the functioning of released FGF-1. Therefore, we analyzed the patterns of oxLDL deposition by using mAb OXL41.1, which specifically recognizes the oxidized form of LDL and does not cross-react with native LDL. We distinguished 2 patterns (Figure 4): in matrix-rich regions containing predominantly viable cells of both SMC and macrophage origin, oxLDL-positive staining was ob-
served intracellularly in many but not in all cells, whereas extracellular depositions of oxLDL were rare (Figure 4A). In contrast, in regions characterized by lower cellularity and the presence of lipid-laden macrophage-derived foam cells and giant cells, cholesterol clefts, and large necrotic areas, diffuse extracellular staining for oxLDL was found in addition to cell-associated staining, and the staining intensity was significantly higher (Figure 4B). Movat’s staining of components of the extracellular matrix revealed that the areas free of extracellular oxLDL frequently showed positive staining for HSPGs, a counterpart of FGF-1 (Figure 4C), whereas the presence of HSPGs was not typical for the regions with intensive extracellular staining for oxLDL (Figure 4D). These results suggest that local predominance of either HSPGs or oxLDL in the extracellular milieu might substantially influence FGF-1 functioning.

To test this hypothesis, we stained the atherectomy specimens for PCNA as a marker of cell proliferation. Regions with weak or absent extracellular staining for oxLDL contained 10- to 20-fold more PCNA-positive cells (reflecting that FGF-1 is mitogenically active) than regions with strong extracellular staining for oxLDL, despite the presence of FGF-1 immunoreactivity. Altogether, the correlations found in human atherosclerotic lesions argue in favor of an FGF-1/oxLDL interaction in vivo, which renders FGF-1 ineffective in promoting cell proliferation.
Discussion

Using molecular sieve and electrophoretic mobility shift assays, we established that FGF-1 forms a tight complex with oxLDL in vitro, whereas its affinity to nonatherogenic, native LDL is low. Because the family of FGFs is defined by their high affinity for heparin, which is crucial for their functioning and conformational stabilization, especially in the case of FGF-1,6,9 the interaction of FGF-1 with oxLDL discovered in this study is of particular interest in the context of the complex atherosclerotic milieu, where all 3 components (the growth factor, lipoproteins, and HSPGs) might be present simultaneously. The affinities of FGF-1 for oxLDL ($K_c=206±9.7$ mmol/L) and heparin ($K_c=41±3.5$ mmol/L) that we determined suggest that the form in which FGF-1 is present in the extracellular environment will depend on local relative concentrations of HSPGs and oxLDL. An HSPG-rich environment favors formation of the high-affinity FGF-1/ HSPG/FGFR complex, whereas foci of high oxLDL accumulation might create conditions that shift FGF-1 binding to oxLDL. The striking finding is that formation of the FGF-1/ oxLDL complex rendered FGF-1 nonmitogenic on both mouse and human SMCs, and its activity could only partially be restored by subsequent addition of heparin. Inhibition of the mitogenic activity of FGF-1 correlated with a dramatically decreased ability of the FGF-1/oxLDL complex to bind heparin, which is consistent with the role of HSPGs in assembly of the FGF-1/FGFR complex.9

Interaction of both the growth factor and the lipoprotein with heparin is provided by ionic contacts between positively charged lysine and arginine residues of FGF-1 (the surface loop 112 to 128)10 or apoB (region 3134 to 3489) of LDL15 and negatively charged sulfate groups of heparin. We hypothesize that the weak interaction of FGF-1 with native LDL is likely due to repulsion between positively charged residues in both FGF-1 and native LDL, so that FGF-1 remains in the unbound form or binds to native LDL via hydrophobic rather than electrostatic bonds. In contrast, the higher net negative charge of oxLDL particle due to oxidative modification of lysine residues16 provides the higher affinity of the FGF-1/ oxLDL complex, which is likely to have an electrostatic nature. The loss of ability of complexed FGF-1 to bind to heparin might be explained by involvement of some residues within the heparin-binding region of FGF-1 in complex formation with oxLDL. Alternatively, complex formation may alter the tertiary structure of FGF-1, which leaves this region inaccessible for interaction with heparin.

Our findings in human atherectomy specimens provide strong evidence for interactions between FGF-1 and lipoproteins in vivo and further elucidate their consequences. First, the highest expression of FGF-1 was detected in macrophages, the cell type mainly responsible for LDL oxidation25 and accumulation of oxLDL.26 Second, our finding of 2 distinct patterns of oxLDL accumulation suggests that the released FGF-1 will encounter an extravascular environment of variable oxLDL content (oxLDL poor or oxLDL rich). Third, regions with massive extracellular deposits of oxLDL had 10- to 20-fold fewer PCNA-positive cells (used as a criterion of cell proliferation) than did oxLDL-poor regions with viable cells and well-elaborated matrix, often HSPG rich. These correlations support the argument that in vivo, there is an inverse relation between the mitogenic activity of FGF-1 and local oxLDL content in the atherosclerotic milieu.

Accumulation of unmodified LDL in the extracellular matrix is typical for early stages of plaque development, whereas with its progression, the balance shifts toward oxLDL.27,28 Based on our results, it is tempting to speculate that LDLs may be viewed as components of the plaque, previously not recognized, which modulate FGF-1 functioning at different stages of plaque progression by facilitating its mitogenic activity in early lesions and by inactivating FGF-1 through complex formation with oxLDL in advanced lesions. With regard to the mechanism of the enhancing effect of native LDL, we hypothesize that repulsion between positive residues in FGF-1 and native LDL imposes a more compact structure on FGF-1, thus facilitating assembly of the FGF-1/ HSPGs/FGFR complex. On the other hand, the inhibitory effect of abundant oxLDL on FGF-1 mitogenicity could be among the reasons for failure to produce a solid fibrous cap over advanced lesions that increases their vulnerability to rupture. In conclusion, our data provide evidence that native LDL and oxLDL, besides being bulky, friable components of the atherosclerotic lesion, also manifest their pathogenicity by interfering with the growth-promoting function of FGF-1 in opposite directions during different phases of atherogenesis.

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References


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