Upregulation of Endothelial Receptor for Oxidized Low-Density Lipoprotein (LOX-1) in Cultured Human Coronary Artery Endothelial Cells by Angiotensin II Type 1 Receptor Activation


Abstract—Cross talk between oxidized LDL (ox-LDL) and angiotensin II (Ang II) may be relevant in atherosclerosis. In this study, we examined the presence of a specific endothelial receptor for ox-LDL (LOX-1) and Ang II receptors in human coronary artery endothelial cells (HCAECs). In addition, we studied the effect of Ang II on LOX-1 gene and protein expression. LOX-1 was consistently identified in HCAECs by reverse transcriptase–polymerase chain reaction (RT-PCR), cDNA sequence, Western blot, and 125I-labeled ox-LDL binding assay (B_max, 29.7 ng/mg protein). The HCAECs also exhibited Ang II receptors (AT_1, AT_2), as determined by RT-PCR and 125I-labeled Ang II binding assay (B_max, 2.21 and 1.19 fmol/mg protein, respectively). Incubation of HCAECs with Ang II markedly increased LOX-1 mRNA (RT-PCR) and protein (Western blot) expression. The increase in LOX-1 expression was dependent on Ang II concentration (10^{-12} to 10^{-6} mol/L). Ang II caused a concentration-dependent increase in 125I-labeled ox-LDL uptake by HCAECs and enhanced ox-LDL–mediated cell injury, as evident from an increase in LDH release and a decrease in cell viability. These effects of Ang II were completely blocked by pretreatment of HCAECs with losartan, a specific AT_1 blocker, but not by PD123319, a specific AT_2 blocker. These observations indicate the following: (1) HCAECs possess abundant LOX-1 as well as Ang II (AT_1, AT_2) receptors, (2) Ang II upregulates LOX-1 receptor and ox-LDL uptake, (3) the effects of Ang II are mediated by AT_1 activation, and (4) Ang II enhances ox-LDL–mediated injury to HCAECs. (Circ Res. 1999;84:1043-1049.)

Key Words: angiotensin II ■ endothelial cell ■ oxidized LDL ■ receptor

Low-density lipoprotein, especially its oxidatively modified form, oxidized LDL (ox-LDL), and angiotensin II (Ang II) are 2 critical factors in atherogenesis. Endothelial dysfunction elicited by ox-LDL has been implicated in the pathogenesis of atherosclerosis its manifestations. LDL is oxidized in vascular endothelial cells into a highly injurious product that results in cellular dysfunction in large arteries and resistant vessels. The endothelial dysfunction (ie, loss of vasodilation, vasoconstriction, thrombosis, and inflammation) occurs before and throughout the development of atherosclerosis and particularly during plaque rupture. ox-LDL appears to induce this cellular dysfunction in a time- and concentration-dependent manner.

Vascular endothelial cells in culture and in vivo internalize and degrade ox-LDL through a putative receptor-mediated pathway that does not seem to involve the classic macrophage scavenger receptor. Sawamura et al cloned the endothelial receptor for ox-LDL (LOX-1), which is a membrane protein that belongs structurally to the C-type selectin family and is expressed in vivo in vascular endothelium and in vascular-rich organs. We have recently identified the presence of LOX-1 in cultured human coronary artery endothelial cells (HCAECs) and demonstrated that ox-LDL upregulates the expression of LOX-1 mRNA and protein. This receptor on bovine endothelial cells is induced by shear stress and by tumor necrosis factor-α and phorbol 12-myristate 13-acetate. Because endothelial uptake of ox-LDL is important in atherosclerosis, further understanding of the regulation of LOX-1 may be of immense clinical significance.

Ang II, like ox-LDL, is an important factor in atherogenesis. Ang II activates at least 2 distinct types of cell-surface receptors, type 1 (AT_1) and type 2 (AT_2). Most experimental studies have shown that it is the AT_1 activation that mediates most of the known effects of Ang II in the cardiac tissues, although in some studies the proapoptotic role of AT_2 has also been demonstrated. Whereas the presence of both AT_1 and AT_2 has been confirmed in coronary artery...
endothelial cells taken from the rat,16 the distribution of Ang II receptors (AT₁ and AT₂) in HCAECs has not yet been defined.

Recent studies suggest an interaction between hyperlipidemia, activation of the renin-angiotensin system, and atherosclerotic disease.16–19 For example, Ang II facilitates oxidation of LDL18 and its uptake by scavenger receptor on monocytes/macrophages.19 It is, however, not clear whether Ang II stimulates uptake of ox-LDL by endothelial cells. We postulated that Ang II may upregulate LOX-1 as a basis of enhanced endothelial uptake of ox-LDL in the presence of Ang II. This study was designed to document the presence of specific endothelial receptors for ox-LDL and Ang II in cultured HCAECs and the regulation of endothelial receptor for ox-LDL by Ang II.

Materials and Methods

Cell Culture

HCAECs (initial batch from Clonetics Corp) were pure, as determined by morphology and staining for factor VIII and acetylated LDL. These cells were 100% negative for α-actin smooth muscle expression. Microvascular endothelium growth medium consisted of 500 mL of endothelial cell basal medium, 5 ng of human recombinant epidermal growth factor, 25 mg of gentamycin, 25 µg of amphotericin B, 6 mg of bovine brain extract, and 25 mL of FBS. HCAECs were seeded in a 25-cm² flask (4000 cells/cm²) and incubated at 37°C in 95% air/5% CO₂. Fifth-generation HCAECs, losartan (10⁻⁶ mol/L), a specific AT₁ blocker, or PD123319 were added to the culture medium before cells were incubated with Ang II (10⁻⁹ to 10⁻⁷ mol/L), ox-LDL (40 µg/mL), or both. In other groups of HCAECs, losartan (10⁻⁶ mol/L), a specific AT₁ blocker, or PD123319 (10⁻⁶ mol/L), a specific AT₂ blocker, was added to the culture medium before cells were incubated with Ang II (10⁻⁶ mol/L), ox-LDL (40 µg/mL), or both. The concentrations of Ang II, losartan, and PD123319 were chosen on the basis of previous studies.12,13

Preparation of Lipoproteins

Native LDL and ox-LDL were prepared as described earlier.21 In brief, human native LDL was isolated from human blood plasma by discontinuous centrifugation. It was purified by ultracentrifugation (1063 to 1.210 g/mL) to homogeneity determined by agarose gel electrophoresis. LDL was oxidized by exposure to CuSO₄ (5 µmol/L free Cu²⁺ concentration) in PBS at 37°C for 24 hours. The thio- bituric acid reactive substances content of ox-LDL was 18.2±0.28 versus 0.56±0.16 nmol/100 µg protein in the native LDL preparation (P<0.01). ox-LDL was oxidatively modified with 125I by the iodine monochloride method.22 It was then purified on a Biogel P-10 column and extensively dialyzed against Tris–saline. LDL, ox-LDL, and 125I-labeled ox-LDL (125I-ox-LDL) were kept in 50 mMol/L Tris–HCl, 0.15 mol/L NaCl, and 2 mmol/L EDTA at pH 7.4 and were used within 10 days of preparation.

Reverse Transcriptase–Polymerase Chain Reaction (RT-PCR) for LOX-1 mRNA Expression

Total RNA (1 µg) extracted from cultured HCAECs was reverse transcribed with oligo(dT) and Moloney murine leukemia virus reverse transcriptase (both from Promega) at 37°C for 1 hour. Reverse-transcribed material (2 µL) was amplified with Taq DNA polymerase (Promega) using a primer pair specific to human endothelial receptor (sense primer, 5'-TTACTCTCCATGGTGCTGCC-3'3; antisense primer, 5'-AGCTTCTTCTGTTGTGGTG-3'). The PCR product was 193 bp. PCR consisted of 40 cycles of 94°C for 40 seconds, 55°C for 1 minute, and 72°C for 1 minute. The RT-PCR–amplified samples were visualized on 1.5% agarose gels using ethidium bromide. In some experiments, human β-actin was amplified as a reference for quantification of LOX-1 mRNA. A primer pair of human β-actin was used (sense primer, 5'-TCTGATATGGAGAGCTATGAGCTGCC-3'; antisense primer, 5'-TCGGATCCGTGCCACCAAGAGCAGACTGGTGTTG-3'). The PCR product was 201 bp. PCR consisted of 40 cycles at 95°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute. Relative intensities of bands of interest were analyzed by the NSF-300G scanner (Microtek) and scan analysis software (Biosoft) and were expressed as ratios to the β-actin mRNA band.

LOX-1 Sequence

The RT-PCR product for direct sequencing was purified using the QIAquick PCR purification kit. Each sequencing reaction (20 µL) contained 14 µL of cDNA (2 to 3 µg), 2 µL of BigDye reaction mix (Perkin Elmer), 1 µL of LOX-1 forward and reverse primers (3.2 pmol/µL), and 3 µL of 5× sequencing buffer (400 nmol/L Tris–HCl and 10 mmol/L MgCl₂, pH 9.0). After 25 cycles of 96°C for 10 seconds, 50°C for 5 seconds, and 60°C for 4 minutes, 1/10 volume of 3 mol/L sodium acetate (pH 5.2) and 3 volumes of 95% ethanol were added to each sequencing reaction. The samples were then centrifuged for 20 minutes at room temperature. The pellet was washed once with 250 µL of 70% ethanol and dried in a vacuum dryer, and then it was dissolved in 20 µL of template suppression reagent (Perkin Elmer). The sequence was then read with an automated DNA sequencer (ABI 310; Applied Biosystems, Inc). The published sequence of LOX-1 was used to compare homologies with the sequence of LOX-1 obtained in this study.

LOX-1 Binding Assay

To examine binding properties of ox-LDL, studies were conducted with cells at 4°C. Cells were prechilled for 30 minutes in HEPES buffer, pH 7.4, before addition of lipoprotein. [125I]ox-LDL was added to each dish for final concentrations of 0.625, 1.25, 2.5, 5, 10, and 15 µg/mL. To determine specific binding of [125I]ox-LDL, a 100-fold excess of unlabeled ox-LDL was added in parallel dishes. Incubation was carried out at 4°C for 2 hours. Cells were washed on ice with 150 mmol/L NaCl, 50 mmol/L Tris, and 2 mmol/L EDTA, pH 7.4, containing 2 mg/mL BSA. The wash schedule consisted of 2 rapid washes, 2 10-minute washes, and a final rapid wash. Cells were then rinsed with cold saline without BSA. Cells were lysed at room temperature in 0.5 mol/L NaOH solution. An aliquot of the cell lysate was counted to determine the amount of bound [125I]ox-LDL.23 Protein was then quantified by BCA protein assay kit. LOX-1 Bmax and Kd were determined by Scatchard plot.4

Western Analysis for LOX-1 in HCAECs

HCAEC lysates from each experiment (20 µg per lane) were separated by 12% SDS-PAGE and transferred to nitrocellulose membranes. After incubation in blocking solution (4% nonfat milk, Sigma), membranes were incubated with a 1:750 dilution monoclonal antibody to human LOX-1 for 2 hours at room temperature. Membranes were washed and then incubated with a 1:3000 dilution of second antibody (Amersham Life Science) for 1 hour, and the membranes were detected with the enhanced chemiluminescence system (Amersham Life Science). Washed membranes were then scanned with a 1000 dilution monoclonal antibody to human β-actin (Sigma). Relative intensities of protein bands were analyzed by scanner (model MSF-300G, Microtek Laboratory).20

RT-PCR for Ang II Receptors

Total RNA (1 µg) extracted from HCAECs was reverse transcribed with oligo(dT) and Moloney murine leukemia virus reverse transcriptase (both from Promega) at 37°C for 1 hour. The reverse-transcribed material (2 µL) was amplified with Taq DNA polymerase (Promega) using a primer pair specific to human AT₁ (forward primer, 5'-TCAATTTAATTTGATTGTTGTA-3'3; reverse primer, 5'-TGAAATTGATTTTGTTTAATGGT-3'). The PCR product was 532 bp. PCR consisted of 40 cycles at 94°C for 1 minute, 50°C for 1 minute,
Uptake of $^{[125]}$Iox-LDL by Ang II

HCAECs were incubated with Ang II ($10^{-12}$ to $10^{-8}$ mol/L) in the presence or absence of losartan or PD123319 for 24 hours. Cells were prechilled for 30 minutes in HEPES buffer, pH 7.4. $^{[125]}$Iox-LDL was added to each dish in a final concentration of 12.5, 25, 50, 100, 200, and 400 pmol/L. Cells were incubated with 1 mL of reaction mixture in the absence and presence of 1 μmol/L unlabeled Ang II, the specific AT$_1$ antagonist losartan, or the specific AT$_2$ antagonist PD123319 to determine total, nonspecific AT$_1$ and AT$_2$ binding, respectively. Incubation was carried out at room temperature for 90 minutes. Cells were then washed in ice-cold PBS, pH 7.2, containing 1% BSA. Cells were then rinsed with cold saline without BSA. Cells were lysed at room temperature for 90 minutes. Cells were then washed in ice-cold PBS, pH 7.2, containing 1% BSA. Cells were then rinsed with cold saline without BSA. Cells were lysed at room temperature in 0.5 mol/L NaOH solution. An aliquot of the cell lysate was counted to determine the amount of bound radiolabeled Ang II antagonist $^{[125]}$I-labeled (Ser1, Ile8) Ang II.

**Sequence of the RT-PCR Product for LOX-1**

$^{151}$-TTACTCTCCA TGGTG66TGCCT GGCTGTGCTAC GACTCTAGGG
gtctttGgc TGAATAGT ATGAGCATT ATGGGTGTCG
GCATGCATT ATCCAGGTT CTGACTTTCC TAACACAGA
GCAAGCAAC CTCACTACCC AGAAAAAGAA ACTGAGGGA
CAGATCTCG CCGCGAACA AGCAGAGAAA GGT

The sequence of the RT-PCR product for LOX-1 is the same as the published original sequence of LOX-1 located at 151 to 343 bp. This result further confirmed the expression of LOX-1 gene in HCAECs. See Materials and Methods for details.

**Measurement of LDH**

One milliliter of sample was collected for determination of LDH. A spectrophotometric enzyme activity method based on the oxidation of lactate was used (Sigma). LDH activity was expressed as units per milligram protein.

**Data Analysis**

All data are presented as mean±SD of duplicate samples from at least 3 independently performed experiments. Statistical significance was determined in multiple comparisons among independent groups of data in which ANOVA and the F test indicated the presence of significant differences. P≤0.05 was considered significant.

**Results**

**LOX-1 Expression in HCAECs**

mRNA for LOX-1 was consistently detected in all HCAECs (n=6) (Figure 1). The sequence of RT-PCR product for LOX-1 in HCAECs was the same as the previously published sequence of LOX-1 location at 151 to 343 bp (Table).

As shown in Figure 2, all aliquots of HCAECs were observed to possess high-affinity $^{[125]}$Iox-LDL binding sites, as determined from a reciprocal plot of the data from triplicate experiments. Scatchard analysis indicated high-affinity LOX-1 binding sites ($B_{max}$, 29.7 ng/mg cell protein; $K_d$, 1.71×$10^{-4}$ mol/L).

**Ang II Receptors in HCAECs**

mRNA for both AT$_1$ and AT$_2$ was detected in all aliquots of cultured HCAECs (n=6). Expression of AT$_1$ mRNA was consistently higher than that of AT$_2$ mRNA (Figure 3). This
observation was supported by Ang II receptor binding assays that showed that HCAECs possess high affinity Ang II binding sites, as determined from a triplicate reciprocal plot of the data. Scatchard analysis indicated that the $K_d$ values of $AT_1$ and $AT_2$ for HCAECs were 168 and 172 pmol, respectively. The $B_{max}$ values of $AT_1$ and $AT_2$ in HCAECs were 2.21 and 1.19 fmol/mg protein, respectively (Figure 4).

**Influence of Ang II on LOX-1 Expression**

Incubation of Ang II with HCAECs increased LOX-1 mRNA (RT-PCR) and protein (Western blot) expression. The increase in LOX-1 mRNA and protein expression was dependent on Ang II concentration ($10^{-12}$ to $10^{-6}$ mol/L).

Importantly, the increase in LOX-1 mRNA expression in response to Ang II was completely blocked by losartan, a specific $AT_1$ blocker, but not by PD123319, a specific $AT_2$ blocker (n=6, Figure 5). The increased LOX-1 protein expression in response to Ang II was also blocked by pretreatment of HCAECs with losartan, but not with PD123319 (n=6, Figure 6).

**Influence of Ang II on ox-LDL Uptake by HCAECs**

Incubation of HCAECs with Ang II increased ox-LDL uptake in a concentration-dependent manner ($10^{-12}$ to $10^{-6}$ mol/L). This effect of Ang II was completely blocked by losartan. In contrast, PD123319 did not change Ang II–mediated ox-LDL uptake by HCAECs. Losartan alone had no effect on the uptake of ox-LDL (Figure 7).

**Cell Viability**

Incubation of HCAECs with Ang II ($10^{-6}$ mol/L) or ox-LDL (40 µg/mL) decreased HCAEC viability compared with control ($P<0.05$). On coincubation, Ang II ($10^{-6}$ mol/L) potentiated the effect of ox-LDL (40 µg/mL) and further decreased cell viability ($P<0.05$). Losartan completely blocked the effect of Ang II, whereas PD123319 had no effect on the cell viability (Figure 8).

**LDH Release in Medium**

Ang II ($10^{-6}$ mol/L) and ox-LDL (40 µg/mL) each increased LDH release in the medium compared with control ($P<0.05$). The presence of both Ang II and ox-LDL caused a marked increase in LDH release compared with Ang II or ox-LDL alone ($P<0.05$). Losartan, but not PD123319, completely prevented the effect of Ang II (Figure 9). These results are...
consistent with the change in cell viability with Ang II and ox-LDL (Figure 8).

Discussion

**ox-LDL Receptors on HCAECs**

Work done in several laboratories implicates LDL, especially its oxidatively modified form, in the pathogenesis of atherosclerosis. In the vascular tissues, ox-LDL attenuates nitric oxide–mediated dilation and promotes leukocyte deposition. ox-LDL also causes changes in the expression of certain genes associated with apoptosis in endothelial cells, such as bcl-2, Fas, and nitric oxide synthase. The presence of abundant high-affinity LOX-1 on human endothelial cells provides a structural basis for incorporation of ox-LDL into these cells and resultant cellular dysfunction. Interestingly, ox-LDL also induces expression of P-selectin on the endothelial cells, and P-selectin and LOX-1 share some structural homology. These observations may have a bearing on ox-LDL–mediated facilitation of leukocyte deposition on blood vessels as well. Other studies from our laboratory indicate that ox-LDL, but not native LDL, upregulates LOX-1 protein and mRNA, suggesting an autoregulatory role of these receptors. These observations imply a critical role of LOX-1 expression in the uptake of ox-LDL and cell injury.

**Figure 8.** Viability of HCAECs in response to Ang II (10^{-6} mol/L) or ox-LDL (40 μg/mL), as determined by trypan blue dye exclusion. There is a decrease in cell viability in response to Ang II or ox-LDL. On coinubcation, Ang II potentiates the effect of ox-LDL. The effect of Ang II is blocked by losartan (10^{-6} mol/L) but not by PD123319 (10^{-6} mol/L). Data are mean±SD from 6 separate experiments.
Ang II Receptors on HCAECs

Both AT1 and AT2 have been identified in normal as well as in failing cardiac tissues.31-32 Most experimental studies have shown that it is the AT1 activation that mediates most of the known effects of Ang II in cardiac tissues.11-14 These include superoxide anion generation, adhesion of monocytes/macrophages, oxidation of LDL, and induction of apoptosis. Accordingly, AT1 activation has been implicated in the pathogenesis of atherosclerosis and coronary heart disease. Actually, a marked increase in AT1 density has been shown in hypercholesterolemic atherosclerosis in rabbits.33 A recent study34 showed a total absence of arrhythmias after a brief period of ischemia-reperfusion in AT1r-knockout mice, further confirming the critical role of AT1 activation in ischemia-reperfusion injury. However, the distribution of AT1 and AT2 in HCAECs has not until now been defined. The present report provides the first definitive evidence for the expression of high-affinity AT1 and AT2 in HCAECs, with a predominance of AT1. The predominance of AT1 was confirmed in the present study by 2 independent methods, RT-PCR and binding assay, and the results of these methods were complementary.

Preliminary studies from our laboratory14 have shown that Ang II induces apoptosis of HCAECs and enhances the cell-injurious effects of anoxia-reoxygenation and tumor necrosis factor-α. These effects of Ang II are mediated primarily via AT1 activation, implying that the expression of AT1 in coronary endothelial cells is linked to endothelial injury. As noted earlier, other studies15 have shown that certain cell types, such as PC12W (rat pheochromocytoma) and R3T3 (mouse fibroblasts), express primarily AT2, and in these cell lines apoptosis is mediated by AT2 activation. It may be speculated that it is the AT1 activation that mediates apoptosis in cell types that express mainly AT2, and it is the AT2 activation that mediates apoptosis in cell types that express mainly AT1.

Interaction Between ox-LDL and Ang II

Several experimental studies in hyperlipidemic animal models have suggested an interaction of the renin-angiotensin system and hypercholesterolemia.17-19 Recent work35 shows that LDL upregulates AT1 gene expression in cultured vascular smooth muscle cells. The AT1 protein expression is increased ∼2-fold in hypercholesterolemic rabbits compared with normocholesterolemic animals. Importance of the upregulation of AT1 synthesis comes from increased vasoconstriction in response to Ang II and loss of endothelium-dependent vasorelaxation.35 In other in vitro studies, Ang II has been shown to enhance the uptake and oxidation of LDL by monocytes and macrophages.18,19 In this study, we demonstrate that Ang II increases uptake of ox-LDL by HCAECs in a concentration-dependent manner. Thus, LDL upregulates AT1 expression in the blood vessels and Ang II enhances LDL uptake in monocytes and ox-LDL uptake in endothelial cells. This interaction (cross talk) suggests a critically important role for the renin-angiotensin system and abnormal lipid levels in blood. Indeed, several clinical studies have shown that inhibition of the renin-angiotensin system and reduction in LDL-cholesterol levels independently, but similarly, improve markers of atherosclerosis and endothelial dysfunction and reduce the number of cardiac events.36,37 Another study39 showed that Ang II administration to mice enhanced ox-LDL uptake by macrophages via its stimulatory effect on cellular proteoglycan content, and this process can lead to foam cell formation and atherosclerosis. An experimental study38 showed that angiotensin-converting enzyme inhibitors significantly attenuate the toxic effect of ox-LDL in aortas of rats.

Upregulation of LOX-1 by Ang II

In the present study, we demonstrate that Ang II upregulates LOX-1 gene and protein expression in cultured HCAECs. These effects of Ang II were completely blocked by losartan, a specific AT1 blocker, but not by PD123319, a specific AT2 blocker. We also show that the enhanced expression of LOX-1 is the basis of increased uptake of ox-LDL by endothelial cells in the presence of Ang II. The blockade of LOX-1 upregulation may be the basis of potent beneficial effect of AT1 blockers in reducing acute cardiac events.36 On the basis of the present study, it is likely that AT1 blockade decreases the uptake of ox-LDL by human coronary arterial tissues by blocking expression of LOX-1. In view of the upregulation of AT1 gene and protein expression in hyperlipidemia, the present observation provides definitive information as to how ox-LDL uptake is increased by AT1 activation. This cross talk between ox-LDL and Ang II may also be clinically relevant, as competitive blockers of AT1 have the potential to block LOX-1 expression and ox-LDL uptake by endothelial cells.

In a recent study,39 LOX-1 expression was found to be upregulated in spontaneously hypertensive rats, an animal model with increased Ang II expression and activity.40 This observation further supports the contention of an interaction between Ang II and ox-LDL.

Cell Injury and the Interaction Between Ang II and ox-LDL

It is widely appreciated that Ang II and ox-LDL are important factors in inducing endothelial dysfunction and injury. Work from our laboratory has shown that Ang II34 and ox-LDL20 decrease nitric oxide generation and increase lipid peroxidation and LDH release in cultured HCAECs. Furthermore, Ang II and ox-LDL enhance anoxia-reoxygenation-mediated HCAEC injury. Work from other laboratories41,42 also suggests that Ang II and ox-LDL causes injury to endothelial cells. In the present study, we demonstrate that the presence of Ang II enhanced ox-LDL-mediated cell injury, as indicated by a decrease in HCAEC viability and increase in LDH release. The mechanism of enhancement of cell injury may be related to the upregulation of LOX-1 mediated by AT1 activation, given that losartan, but not PD123319, inhibited the stimulatory effect of Ang II on ox-LDL-mediated cell injury. These data also provide a basis for suggesting that AT1 blockers may inhibit ox-LDL-mediated injury in clinical disease states.

In summary, this study shows that HCAECs possess abundant endothelial receptors for ox-LDL (LOX-1) as well as Ang II. Ang II upregulates LOX-1 mRNA and protein expression via activation of AT1. These observations may
have important implications with regard to propagation of atherosclerosis and its therapy.

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References
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