Angiotensin II Induces Monocyte Chemoattractant Protein-1 Gene Expression in Rat Vascular Smooth Muscle Cells

Xi-Lin Chen,* Pradyumna E. Tummala,* Matthew T. Olbrych, R. Wayne Alexander, Russell M. Medford

Abstract—Monocyte infiltration into the vessel wall, a key initial step in the process of atherosclerosis, is mediated in part by monocyte chemoattractant protein-1 (MCP-1). Hypertension, particularly in the presence of an activated renin-angiotensin system, is a major risk factor for the development of atherosclerosis. To investigate a potential molecular basis for a link between hypertension and atherosclerosis, we studied the effects of angiotensin II (Ang II) on MCP-1 gene expression in rat aortic smooth muscle cells. Rat smooth muscle cells treated with Ang II exhibited a dose-dependent increase in MCP-1 mRNA accumulation that was prevented by the AT1 receptor antagonist losartan. Ang II also activated MCP-1 gene transcription. Inhibition of NADH/NADPH oxidase, which generates superoxide and H2O2, with diphenylene iodonium or apocynin decreased Ang II–induced MCP-1 mRNA accumulation. Induction of MCP-1 gene expression by Ang II was inhibited by catalase, suggesting a second messenger role for H2O2. The tyrosine kinase inhibitor genistein and the mitogen-activated protein kinase kinase inhibitor PD098059 inhibited Ang II–induced MCP-1 gene expression, consistent with a mitogen-activated protein kinase-dependent signaling mechanism. Ang II may thus promote atherogenesis by direct activation of MCP-1 gene expression in vascular smooth muscle cells. (Circ Res. 1998;83:952-959.)

Key Words: angiotensin II ■ monocyte chemoattractant protein-1 ■ vascular smooth muscle cell ■ AT1 receptor

The earliest recognizable lesion of atherosclerosis is the “fatty streak,” which partly consists of an aggregate of lipid-laden macrophages (foam cells) within the intimal wall. Monocyte infiltration into the vessel wall is a key initial step in the formation of the atherosclerotic lesion. The recruitment of these macrophages to the lesion is mediated initially by an increased gradient of chemotactic activity and is followed by monocyte adherence to the endothelium and migration into the neointima. Monocyte chemoattractant protein-1 (MCP-1) is chemotactic for monocytes both in vitro and in vivo. MCP-1 has been detected in atherosclerotic lesions from both human and experimental animals but not in normal arteries, suggesting that it may play a significant role in the pathogenesis of atherosclerosis.

Hypertension is an established risk factor for the development of atherosclerosis, but the underlying molecular and cellular mechanisms are unclear. Several lines of experimental and clinical evidence suggest a potential role of the renin-angiotensin system in contributing to the pathogenesis of atherosclerosis. Epidemiological studies suggest that hypertensive patients with an activated renin-angiotensin system have a higher incidence of myocardial infarction than other forms of hypertension. Treatment of patients with left ventricular dysfunction with angiotensin-converting enzyme (ACE) inhibitors reduces the incidence of recurrent myocardial infarction and mortality. ACE inhibitors reduce atherosclerotic lesions in several animal models, including Watanabe hyperlipidemic rabbits, cholesterol-fed minipigs, monkeys, and mice.

Angiotensin II (Ang II), an important component of the renin-angiotensin system and a vasoactive peptide, exerts numerous effects on the cardiovascular system. In addition to its vasoconstrictor role, Ang II directly induces oxidative stress in the vasculature. It generates superoxide anions by activating membrane-bound NADH/NADPH oxidase in cultured rat aortic smooth muscle cells (RASMCs) and in aortas of rats made hypertensive by Ang II infusion. Cytokine-induced MCP-1 gene expression is regulated through an oxidation-reduction (redox)-sensitive mechanism. In this study, we tested the hypothesis that Ang II may contribute to atherosclerosis through induction of oxidative stress and redox-sensitive inflammatory gene expression in the vasculature. Our results demonstrate the following: (1) Ang II stimulates MCP-1 gene expression in cultured RASMCs through an AT1 receptor-mediated mechanism; (2) this induction is dependent on redox-sensitive signaling events; and (3) this induction is dependent on protein tyrosine kinase inhibitors. 

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phosphorylation and activation of a mitogen-activated protein kinase (MAP kinase) cascade.

Materials and Methods

Materials

Ang II, genistein, N-acetyl cysteine (NAC), and H2O2 were obtained from Sigma Chemical Co. Ang II was also obtained from Calbiochem. Losartan was kindly provided by Ronald D. Smith, PhD (DuPont Pharmaceutical Co). PD123319 and PD098059 were obtained from Research Biochemicals International. Diphenylene iodonium (DPI) was obtained from Toronto Research Chemicals, Inc. Diethylamine-nitric oxide (DETA-NO) was obtained from Alexis Biochemicals Corp. Pyrrolidine dithiocarbamate (PDTC) was obtained from Fluka Biochemical Corp. Catalase was obtained from Boehringer Mannheim Corp. Pervanadate was prepared as previously described.24 All batches of Ang II were tested, and found negative, for the presence of endotoxin using a Limulus amebocyte lysate assay kit (ICN Pharmaceuticals).

Cell Culture

RASMCs were generously provided by Dr K.K. Griendling as well as Dr P. Delafontaine (Division of Cardiology, Emory University School of Medicine). RASMCs were isolated from male Sprague-Dawley rat thoracic aortas by enzymatic digestion and were characterized to be vascular smooth muscle cells as previously described.25 RASMCs were grown in DMEM (Gibco Chemical Co) supplemented with 10% FBS, L-glutamine, penicillin (100 U/mL), and streptomycin (100 μg/mL). All experiments were conducted on cells at passages 5 to 15. RASMCs were serum-starved for 24 hours by incubating 95% confluent cells in DMEM with 0.1% FBS. Cell cultures were incubated at 37°C in a humidified atmosphere of 5% CO2 -95% air.

Preparation of RNA and Northern Blot Analysis

Total cellular RNA was isolated by a single extraction using TriPure reagent (Boehringer Mannheim), and 15 μg were size-fractionated using 1% agarose-formaldehyde gels in the presence of 1 μg/mL ethidium bromide. The RNA was transferred to a nitrocellulose membrane, hybridized with 32P-labeled rat MCP-1-specific cDNA, and visualized by autoradiography. Two independent experiments showed similar results. B. Total RNA was isolated from untreated or Ang II-treated (100 nmol/L) RASMCs at indicated times. MCP-1 mRNA levels were determined by Northern analysis as described in panel A. Two independent experiments showed similar results. C. Conditioned medium was collected at 12 and 24 hours after Ang II (100 nmol/L) treatment. MCP-1 levels were determined by ELISA as described in Materials and Methods. Values represent mean±SEM (n=4). *P<0.05 vs control group (CTL).

ELISA for MCP-1

Rat MCP-1 concentration was determined by ELISA, with recombinant rat MCP-1 used as a standard as previously described.26 Briefly, flat-bottomed 96-well ELISA plates (CorningCostar) were coated with 100 μL/well of goat anti-MCP-1 antibody (Santa Cruz Biotechnology Inc, 1 μg/mL in 0.6 mol/L NaCl, 0.26 mol/L H3BO3, and 0.08 N NaOH [pH 9.6]) for 16 hours at 4°C and then washed with PBS and 0.05% Tween (wash buffer). This buffer was used to wash the plates throughout the assay. Nonspecific binding sites were
blocked with incubation in 2% BSA in PBS for 90 minutes at 37°C. The plates were washed 3 times. Then, cultured medium (neat and 10-fold concentrated, 100 μL) from each sample was added and incubated for 1 hour at 37°C. A serial dilution of recombinant rat MCP-1 (PeproTech Inc, 10 to 120 ng/mL) was used to obtain a standard curve. The plates were washed and rabbit anti-rat MCP-1 antibody (PeproTech Inc, 0.5 μg/mL) was added and incubated for 30 minutes at 37°C. This was followed by secondary binding with a horseradish peroxidase-conjugated goat anti-rabbit IgG antibody. Quantification was performed by determination of colorimetric conversion at 450 nm of 3,3′,5,5′-tetramethylbenzidine. The standard concentration curve for MCP-1 measured by this method was linear from 10 to 120 ng/mL. Using this technique, MCP-1 protein could only be detected in 10-fold concentrated medium from Ang II–treated cells. Thus, 10-fold concentrated medium was used to determine MCP-1 levels in all experiments. Conditioned medium was concentrated using Centriprep-10 Concentrators (Amicon).

**Nuclear Run-on Transcription Assays**

RASMCs were treated with or without Ang II (100 nmol/L) for 1 hour, and nuclei were isolated. Nuclear run-on assays were performed with 3×10³ cells/treatment as previously described. For each assay, nuclei were resuspended in 300 μL of transcription buffer containing 100 μCi of [α-32P]UTP and incubated for 30 minutes at 30°C. The labeled RNA was purified by single extraction using TriPure and hybridized to a nylon membrane filter that contained alkali-denatured target cDNA. The filters were prepared by slot blotting of 5 μg of target cDNA and covalently linked by UV irradiation using a Stratalinker UV cross-linker. The cDNAs used were the 700-bp EcoRI fragment of rat MCP-1 cDNA and the 1.2-kb PstI fragment of rat GAPDH cDNA.

**Results**

**Ang II Induces MCP-1 mRNA Accumulation and Secretion of MCP-1 in Cultured RASMCs**

To investigate whether Ang II can directly increase MCP-1 mRNA accumulation, serum-starved RASMCs were treated with or without Ang II for 6 hours. By Northern analysis,
there was little MCP-1 mRNA expression in unstimulated RASMCs (Figure 1A, lane 1). Ang II induced a dose-dependent increase in MCP-1 mRNA accumulation. There was a 3.4-fold increase in MCP-1 mRNA accumulation with 1 nmol/L Ang II (lane 2), and maximal induction by Ang II occurred at a concentration of 10 nmol/L (lane 3). The increase in MCP-1 mRNA levels could be detected after 1 hour of Ang II stimulation, peaking at 4 hours and returning to baseline at 24 hours after Ang II treatment (Figure 1B). To examine whether the increase in MCP-1 mRNA levels in response to Ang II is associated with an increase in MCP-1 production, MCP-1 protein levels in the media were determined by ELISA. Extracellular MCP-1 protein concentration increased markedly from 0.03 ng/mL to 3.2 ng/mL and 4.4 ng/mL after 12 hours and 24 hours of Ang II stimulation in RASMCs, respectively (Figure 1C).

**Ang II–Induced MCP-1 mRNA Expression in RASMCs Is Blocked by AT 1 Receptor Blockade**

To determine whether Ang II–induced MCP-1 gene expression is mediated by the AT 1 receptor, RASMCs were pretreated with the AT 1 receptor antagonist losartan. One hundred-fold molar excess of losartan prevented the increase in MCP-1 mRNA accumulation caused by Ang II (100 nmol/L; Figure 2, lane 4). Losartan had no effect on tumor necrosis factor-α (TNF-α)-induced MCP-1 mRNA expression (lane 5). Pretreatment of RASMCs with 100-fold molar excess of the AT 2 receptor antagonist PD123319 had no effect on an increase in MCP-1 mRNA expression (data not shown). These data suggest that the induction of MCP-1 gene expression by Ang II is mediated through AT 1 receptors in RASMCs.

**Ang II Induces MCP-1 Gene Transcription in RASMCs**

To investigate whether Ang II can induce MCP-1 gene transcription, nuclear run-on experiments were performed. RASMCs were treated with Ang II (100 nmol/L) for 1 hour, nuclei were isolated, and radiolabeled RNA generated by these nuclear preparations was hybridized to rat MCP-1 cDNA or rat GAPDH cDNA. There was low basal hybridization in nontreated RASMCs (Figure 3). When RASMCs were treated with Ang II, there was a 2-fold increase in MCP-1 gene transcription. These data suggest that Ang II induces MCP-1 gene transcription in RASMCs.

**Ang II–Induced MCP-1 Gene Expression in RASMCs Is Abolished by Inhibitors of Membrane-Bound NADH/NADPH Oxidase**

Previous studies showed that Ang II activates membrane-bound NADH/NADPH oxidase and generates superoxide anions in RASMCs. To determine whether this activation plays a role in MCP-1 gene expression, we pretreated cultured RASMCs with 2 inhibitors of flavin-binding proteins, DPI (40 μmol/L) and apocynin (200 μg/mL), for 1 hour, followed by Ang II (100 nmol/L) for 6 hours. As determined by Northern analysis, both DPI and apocynin inhibited MCP-1 mRNA accumulation in RASMCs stimulated with Ang II (Figure 4). These data suggest that NADH/NADPH oxidase is involved in Ang II–induced MCP-1 gene expression.

**H 2 O 2 as a Mediator in Ang II–Induced MCP-1 Gene Expression in RASMCs**

Because superoxide generated by NADH/NADPH oxidase can be converted spontaneously or enzymatically to H 2 O 2 , we
tested whether H$_2$O$_2$ plays a direct role in Ang II–induced MCP-1 gene expression in RASMCs. RASMCs were exposed to H$_2$O$_2$ (25 to 100 μmol/L) for 3 hours. H$_2$O$_2$ induced a dose-dependent increase in MCP-1 mRNA accumulation in RASMCs after 3 hours of incubation (Figure 5A). To examine whether endogenously generated H$_2$O$_2$ is involved in the signaling pathway for Ang II–induced MCP-1 gene expression, we pretreated RASMCs with or without catalase (3000 U/mL) for 24 hours and then treated the cells with Ang II (100 nmol/L) for 6 hours. MCP-1 mRNA levels were determined by Northern analysis. Three independent experiments showed similar results.

Nitric Oxide Inhibits Ang II–Induced MCP-1 mRNA Accumulation in RASMCs

In endothelial cells, exogenous nitric oxide (NO) inhibits cytokine-induced expression of redox-sensitive genes such as vascular cell adhesion molecule-1 and MCP-1. To examine whether NO can similarly inhibit Ang II–induced MCP-1 mRNA accumulation, RASMCs were pretreated with or without the NO donor, DETA-NO (100 μmol/L), for 1 hour. Pretreatment with DETA-NO decreased Ang II–induced MCP-1 mRNA accumulation (Figure 6, lane 4). DETA alone had no effects on basal or Ang II–induced MCP-1 mRNA expression (data not shown).

Thiol Antioxidants Did Not Block Ang II–Induced MCP-1 mRNA Accumulation in RASMCs

To examine whether thiol antioxidants can inhibit Ang II–induced MCP-1 gene expression, RASMCs were pretreated with the thiol antioxidants PDTC (100 μmol/L) or NAC (5 mmol/L) for 1 hour. Both of these antioxidants inhibit TNF-α–induced MCP-1 gene expression in cultured endothelial cells. However, neither PDTC nor NAC inhibited Ang II–induced MCP-1 mRNA accumulation in RASMCs (Figure 7A and 7B). Furthermore, NAC by itself strongly induced MCP-1 mRNA (Figure 7B).

Ang II–Induced MCP-1 Gene Expression Requires Both Tyrosine Kinase and MAP Kinase Activities

Ang II induces protein tyrosine phosphorylation in vascular smooth muscle cells. This signaling event mediates Ang II–induced increases in plasminogen activator inhibitor (PAI)-1 and PAI-2 mRNA expression in RASMCs. However, it is unclear whether a similar signaling pathway mediates Ang II–induced MCP-1 gene expression. To determine whether an increase in tyrosine phosphorylation induces MCP-1 mRNA accumulation, RASMCs were exposed to the protein tyrosine phosphatase inhibitor pervanadate (25 to 200 μmol/L) for 3 hours. Pervanadate induced an increase in MCP-1 mRNA accumulation in RASMCs at 25 μmol/L with maximal effects at 100 μmol/L (Figure 8A). This suggests that increased protein tyrosine phosphorylation can induce MCP-1 mRNA accumulation. To determine the involvement of protein tyrosine kinase in Ang II–induced MCP-1 expression, RASMCs were pretreated with or without the specific tyrosine kinase inhibitor genistein (30 μmol/L) for 30 minutes and throughout the experiment. Genistein alone had no effect on basal MCP-1 mRNA levels (Figure 8B, lane 3). Ang II–induced MCP-1 mRNA accumulation was completely inhibited by genistein (Figure 8B, lane 4).
MAP kinases are important mediators of growth factor signal transduction. Ang II is a strong activator of MAP kinase in RASMCs. To investigate whether activation of MAP kinase is involved in Ang II–induced MCP-1 mRNA expression, RASMCs were pretreated with the MAP kinase inhibitor PD098059 (5 to 30 μmol/L) for 30 minutes. PD098059 alone had no effect on MCP-1 mRNA expression (Figure 9, lane 3). Pretreatment with PD098059 inhibited Ang II–induced MCP-1 mRNA expression in a dose-dependent manner. This suggests that activation of a MAP kinase may play an important role in Ang II–induced MCP-1 expression in RASMCs.

**Discussion**

In the present study, we have demonstrated that Ang II is a potent stimulator of MCP-1 expression in cultured vascular smooth muscle cells. Ang II induced MCP-1 mRNA accumulation rapidly and with significant magnitude. Dose-response studies demonstrated a significant induction of MCP-1 mRNA levels at a physiological concentration of Ang II (1 nmol/L). Its maximal effect concentration at 10 nmol/L is similar to, or lower than, other Ang II actions that have been reported. We have also shown that Ang II–induced MCP-1 gene expression occurs through an AT1 receptor-mediated mechanism and at least partially through increased transcriptional activity, as demonstrated by our nuclear run-on experiments.

The regulation of MCP-1 gene expression by cytokines occurs through redox-sensitive transcriptional mechanisms. Similarly to cytokines, Ang II–mediated MCP-1 gene expression may also be coupled to the activation of redox-sensitive transcription factors. Ang II induces oxidative stress by stimulating superoxide anion generation through membrane-bound NADH/NADPH oxidase in cultured RASMCs and in aortas of rats made hypertensive with Ang II. In this study, DPI and apocynin, 2 inhibitors of NADH/NADPH oxidase, suppressed Ang II–induced MCP-1 mRNA accumulation in RASMCs. Flavin-binding protein inhibitors such as DPI block Ang II–induced generation of superoxide. These data suggest that reactive oxygen species generated by flavin-binding proteins such as NADH/NADPH oxidase may be involved in the signaling cascade for Ang II–induced MCP-1 gene expression in RASMCs.

Superoxide anion can be converted spontaneously or enzymatically into H2O2. Both Ang II and H2O2 induce expression of c-fos and c-jun, nuclear activator protein-1 (AP-1) binding activity, and nuclear factor κB (NF-κB) binding activity. In this study, we demonstrated that H2O2 induces MCP-1 gene expression similarly to Ang II in RASMCs. Furthermore, pretreatment of RASMCs with catalase, under conditions that inhibit intracellular H2O2 generation, suppressed Ang II–induced MCP-1 mRNA accumulation. These results suggest that H2O2 may play an important role as a second messenger in upregulating MCP-1 gene expression.

In endothelial cells, cytokines induce the expression of inflammatory genes such as MCP-1 and vascular cell adhesion molecule-1 through oxidative signals involving reactive oxygen species. Exogenously administered NO inhibits this induction, probably through antioxidant effects and inhibition of NF-κB activation. The present study demonstrated that Ang II–induced MCP-1 gene expression is inhibited by an NO donor (DETA-NO) in RASMCs. These findings suggest that a relatively large production of NO can attenuate redox-sensitive inflammatory gene expression in RASMCs. NO is a free radical with both antioxidant and prooxidant properties depending on its relative concentration to other reactive species, such as superoxide anion. NO inhibits cellular superoxide-mediated lipoprotein oxidation.

It is possible that NO inhibits MCP-1 gene activation by decreasing H2O2 via interaction with superoxide to generate peroxynitrite. Alternatively, NO may suppress MCP-1 gene activation by inhibition of NF-κB activation.

Whereas thiol antioxidants inhibit MCP-1 gene expression in response to a variety of proinflammatory stimuli in endothelial cells, an important finding in this study is their inability to inhibit the induction of MCP-1 gene expression by Ang II in RASMCs. These varying sensitivities to antioxidants may reflect differences in cell type, whereby RASMCs may have unique intracellular pathways of thiol antioxidant metabolism. Consistent with this possibility, we have also observed that PDTC and NAC do not inhibit TNF-α–induced MCP-1 gene expression in RASMCs (unpublished observation).

Recent data demonstrated that H2O2 mediates PDGF-induced protein tyrosine phosphorylation and activation of MAP kinase in vascular smooth muscle cells. Ang II increases protein tyrosine phosphorylation and tyrosine kinase-dependent PAI-2 gene expression in vascular smooth muscle cells.

Protein tyrosine kinase is also involved in activation of AP-1 DNA binding activity in myogenic cells by Ang II and in activation of NF-κB by cytokines. The present study suggests a potential signaling role of protein phosphorylation via tyrosine kinase in Ang II–mediated MCP-1 gene expression.

MAP kinases encoded by the extracellular signal-regulated kinase (ERK) genes are a family of serine/threonine protein kinases activated as early responses to a variety of stimuli involved in cellular growth, transformation, and differentiation. They are also involved in activation of AP-1 and NF-κB. Two isoforms of ERK, referred to as p44ERK (ERK1) and p42ERK (ERK2), are activated by phosphorylation of threonine and tyrosine residues by MAP kinase kinase, also called MEK.

Ang II rapidly activates MAP kinases, particularly ERK1 and ERK2, in vascular smooth muscle cells. Using a specific inhibitor of MEK activation, we demonstrated that Ang II–induced MCP-1 mRNA occurs through a PD098059-sensitive MEK. H2O2 appears to be an upstream signal in PDGF-induced protein tyrosine phosphorylation and activation of MAP kinase in vascular smooth muscle cells.

Consistent with our data, it is possible that H2O2 may activate protein tyrosine kinase and MAP kinase and mediate Ang II–induced MCP-1 gene expression.

A variety of experimental and clinical studies suggest the importance of the renin-angiotensin system in atherogenesis. Hypertensive patients with high renin profiles, who are likely to be associated with increased Ang II levels, have a higher risk for myocardial infarction than those with low renin profiles. Patients with the DD ACE genotype have significantly higher levels of ACE activity and increased incidence
of myocardial infarction than those without this genotype. Several recent clinical studies independently demonstrated significant reductions in mortality and morbidity, including decreased recurrent ischemic events, in patients treated with ACE inhibitors after suffering a myocardial infarction. Capers et al have demonstrated a marked inflammatory response, characterized by the infiltration of monocytes/macrophages in the arterial walls of rats made hypertensive by infusion of Ang II. Monocyte/macrophage infiltration also occurs in the arterial walls of spontaneously hypertensive rats but is abolished with treatment with ACE inhibitors. These results and the data from the present study suggest that the proatherogenic properties of the renin-angiotensin system may occur, in part, through Ang II–mediated induction of vascular inflammatory genes such as MCP-1.

Taubman et al and Poon et al reported that Ang II has no effects on JE/MCP-1 mRNA accumulation or monocyte chemoattractant activity in cultured RASMCs. The discrepancy in these results compared with those of our study may lie in the phenotypic heterogeneity of RASMC preparations. For example, Taubman et al and Poon et al reported that thrombin does not stimulate MCP-1 gene expression or monocyte chemoattractant activity in RASMCs, whereas Wenzel et al reported that thrombin is a strong stimulator of MCP-1 expression and monocyte chemoattractant activity in RASMCs. We have addressed this issue of phenotypic heterogeneity by examining 2 independently derived RASMC preparations. Ang II increased MCP-1 mRNA levels in both RASMC preparations. Differences in cell isolation and preparation, culture conditions, and other factors may all have contributed to the discrepancy in the results between this study and that of Taubman et al. In the study of Taubman et al, Ang II treatment increased MCP-1 mRNA half life but decreased MCP-1 gene transcription. The net effect was no change in MCP-1 mRNA levels in Ang II–treated cells. We have similarly observed that Ang II increased MCP-1 mRNA stability (data not shown), but we demonstrated that Ang II can activate MCP-1 gene transcription. We and others have further demonstrated previously that when rats are made hypertensive by infusion with Ang II, there is marked increase in MCP-1 mRNA levels in rat aortas. Given that 95% of the cell population in the aorta consists of vascular smooth muscle cells, these data support our tissue culture studies and suggest that Ang II can stimulate MCP-1 gene expression in vascular smooth muscle cells.

In summary, our results demonstrate that Ang II, a potent vasoconstrictor and growth factor, directly stimulates MCP-1 gene expression in the vasculature via the AT1 receptor. This activation occurs through a redox-sensitive mechanism that appears to involve the activation of membrane-bound NADH/NADPH oxidase through generation of H2O2 as a second messenger. The activation of protein tyrosine kinases and that of MAP kinases also appear to be important signaling events that mediate Ang II–induced MCP-1 gene expression in RASMCs. These proinflammatory effects of Ang II may contribute to atherogenesis by promoting migration of monocytes into the vessel wall. Finally, these results may begin to provide a molecular link between hypertension, a principal risk factor for coronary artery disease, and the development of atherosclerosis.

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