New Perspectives in Hypertension Research
Potentials of Vascular Biology

Victor J. Dzau, Gary H. Gibbons, Ryuichi Morishita, Richard E. Pratt

Abstract The vessel wall was once considered to be a passive conduit responding to the circulating endocrine system. However, the emergence of molecular and vascular biology in hypertension research has redefined our understanding of the role of the vasculature as a vital organ in the pathogenesis of disease. It is now recognized that the vasculature can regulate its own tone by a variety of previously unknown autocrine and/or paracrine vasoactive systems. Recent evidence indicates that the process of vascular remodeling in hypertension appears to be mediated by locally generated factors within the vessel wall. This review examines the implications of this new paradigm in hypertension, focusing on five topics that have developed through the emergence of molecular vascular biology: the discovery and characterization of novel biologically active molecules synthesized by the vessel wall, the molecular mechanisms and consequences of vascular remodeling, the developmental biology of the blood vessel and the relationship to pathobiology, the use of in vivo gene transfer to test hypotheses in vivo, and novel treatment strategies based on gene therapy of the vessel wall. (Hypertension. 1994;23[part 2]:1132-1140.)

Key Words • muscle, smooth, vascular • transfection • gene therapy

Over the past half century, the direction of hypertension research has been shaped by a scientific paradigm that has focused on the regulation of systemic neuroendocrine vasoactive systems that control vascular tone and renal fluid-electrolyte homeostasis. This paradigm postulates that hypertension is caused by a disturbance in the physiological homeostatic mechanisms regulating the levels of and/or responses to circulating hormones and sympathetic nervous system activity. In this schema the vasculature is conceptualized as a simple effector system that passively responds to the actions of systemic neuroendocrine factors. However, advances in molecular vascular biology have begun to promote a paradigm shift that has dramatically altered our conception of the role of the vasculature in hypertension. Based on recent studies it has become increasingly clear that the vasculature is itself a complex, integrated organ capable of autonomous generation of locally active factors that mediate changes in tone and structure. This review will examine the implications of this new molecular vascular biology paradigm in hypertension research, focusing on five areas in which vascular biology has had or will have major effects on hypertension research: (1) the discovery of novel endogenous biologically active molecules synthesized by the vessel walls (2) the elucidation of molecular mechanisms and consequences of vascular remodeling in hypertension, (3) an understanding of the developmental biology of the blood vessel and the relation to pathobiology, (4) the in vivo testing of in vitro hypotheses using in vivo gene transfer, and (5) the development of novel treatment strategies based on vascular molecular biology, such as gene therapy.

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data indicate that the regulation of nitric oxide generation by the endothelium may be a critical determinant of blood pressure in hypertension.

Advances in vascular biology have also reshaped our understanding of previously characterized classic hormonal systems. For example, it has been recognized that a paracrine vascular natriuretic peptide system exists in addition to the classic endocrine system. It is speculated that the recently discovered endothelium-derived type C natriuretic peptide may be an important paracrine system regulating vascular tone and structure. Similarly, the endocrine renin-angiotensin system has been recognized for nearly 100 years, yet the importance of an autocrine-paracrine vascular angiotensin system has been appreciated only within the past decade. The technologies of molecular biology have defined the components of the enzymatic cascade necessary for the local generation of angiotensin II (Ang II) within various tissues, including the vasculature. Mullins et al have developed transgenic rats that exhibit increased vascular ACE expression. Our data indicate that vascular ACE is a key rate-limiting step in local Ang II generation and that the increase in vascular ACE is sufficient to induce Ang II-induced vascular cell growth and vessel wall hyper trophy without concomitant changes in systemic blood pressure or the endocrine renin-angiotensin system. Similarly, we have recently used a novel experimental approach utilizing in vivo gene transfer technology to transfer the ACE gene into the vessel wall and thereby increase local ACE expression. Our data indicate that vascular ACE is a key rate-limiting step in local Ang II generation and that the increase in vascular ACE is sufficient to induce Ang II-induced vascular cell growth and vessel wall hypertrophy without concomitant changes in systemic blood pressure or the endocrine renin-angiotensin system. These studies indicate that autocrine-paracrine vasoactive systems have evolved in parallel with classic endocrine systems and appear to play complementary regulatory roles in vascular homeostasis.

Endothelin-1 is yet another example of a vasoactive molecule that was previously unknown little more than a decade ago. Its potency and long-lived vasoconstrictive effects fueled speculation that it may be an important mediator of hypertension. With the recent emergence of specific endothelin-1 antagonists, we anticipate that the role of endothelin-1 in hypertension will be further characterized. We speculate that similar to the experience with other vascular paracrine systems, the measurement of plasma levels will underestimate the role of endothelin-1 in the pathogenesis of various vascular disorders. Other vessel wall paracrine systems include the kallikrein-kinin system, prostanoids, and endothelium-derived hyperpolarizing factors. Moreover, the vascular biology paradigm would predict that the effects of vasoactive substances such as endothelin on vascular cell growth and vessel structure may be as important in the pathogenesis of hypertension as the effects on vessel tone.

In association with this expanding list of autocrine-paracrine mediators is a growing appreciation of their pleiotropic effects on cell function. It is now clear that vasoactive substances modulate cell growth, migration, matrix production and degradation, thrombosis, and leukocyte adhesion in addition to their effects on vascular tone. These multifunctional properties may partly reflect the multiplicity of cellular receptors and signaling pathways activated by these vasoactive agents. It is of interest that there are three types of natriuretic peptide receptors (A, B, and C), at least three types of angiotensin receptors (AT1A, AT1B, and AT2), and at least two types of endothelin receptors (ETa and ETb). It is intriguing that the expression of these receptors is altered by changes in cell differentiation or phenotype that occur during ontogeny or in response to vascular injury. We speculate that the regulation of vasoactive peptide receptor expression may be an important factor in the pathogenesis of vascular diseases.

Based on exciting new evidence we can now conceptualize the vasculature as an integrated vital organ capable of sensing environmental cues and producing appropriate biologic mediators to modulate tone and structure. We anticipate that further investigation of the vascular biology of autocrine-paracrine factors in hypertension will provide important new insights into the pathogenesis and treatment of this disease.

**Vascular Remodeling in Hypertension**

An emerging concept in hypertension pathophysiology is the contribution of vascular structural changes (vascular remodeling). Vascular biology research has played an important role in elucidating the mechanisms and pathophysiology of vascular remodeling. It is now recognized that, in addition to being able to change its tone acutely, the blood vessel is capable of altering its structure chronically in response to specific conditions (Table 1). This is mediated by an active process that results in a change in the blood vessel geometry. Vascular remodeling is usually an adaptive process in response to chronic changes in hemodynamic conditions and/or humoral factors. However, this process may contribute to the pathophysiology of vascular diseases and circulatory disorders. As will be discussed in detail below, an important concept in the context of hypertension is that vasoactive substances themselves may play a direct role in vascular remodeling. We have previously

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**Table 1. Spectrum of Vascular Remodeling**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Clinical Example</th>
<th>Vascular Response</th>
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<tbody>
<tr>
<td>↑ Pressure</td>
<td>Chronic hypertension</td>
<td>(a) ↑ Wall thickness, ↓ lumen diameter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) ↔ Wall thickness, ↓ lumen diameter</td>
</tr>
<tr>
<td>↑ Flow</td>
<td>Arteriovenous fistula</td>
<td>↑ Inner diameter, ↑ outer diameter</td>
</tr>
<tr>
<td>↓ Flow</td>
<td>After stenosis</td>
<td>↓ Inner diameter, ↓ outer diameter</td>
</tr>
<tr>
<td>Injury</td>
<td>Balloon angioplasty</td>
<td>Myointimal hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Risk factors (LDL cholesterol, smoking, diabetes, etc)</td>
<td>Atherosclerosis</td>
</tr>
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LDL indicates low-density lipoprotein.
hypothesized that most endogenous vasoconstrictive substances are also growth promoters and most endogenous vasodilator substances are growth inhibitors.32,33 Accordingly, vasoactive substances can regulate vascular homeostasis via its short-term effects on vascular tone and its long-term effects on vascular structure. In hypertension, an imbalance of these factors favors vasoconstriction and vascular hypertrophy.

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Table 1 summarizes the broad spectrum of geometric and structural alterations of the blood vessel. A blood vessel can achieve an increase in mass, leading to a thickening of the wall (eg, in hypertension). In this case, the intimal and/or medial layers may increase in size and the inner diameter decrease. Consequently, the ratio of diameters of the wall to lumen increases. Hypertensive vascular hypertrophy resulting from an increase in smooth muscle mass may amplify the vasoconstrictive response to neurohormones and may perpetuate hypertension by accentuating systemic vascular resistance. These changes within hypertensive vessels are seen primarily in small arteries and arterioles, although the large vessels also undergo remodeling involving cellular hypertrophy and matrix changes.34,35 In these large vessels the functional changes are primarily expressed as decreases in compliance and distensibility. An increased wall-to-lumen ratio with encroachment of the lumen may also occur in hypertensive resistance vessels without the increase in medial smooth muscle cell mass as described by Mulvany,34 Baumbach and Heistad,36 and others. This is accomplished primarily by a rearrangement of the smooth muscle and other cellular and noncellular elements, resulting in a primary reduction of the diameter.

Another form of remodeling relevant to hypertension is that of enlargement or dilation of the blood vessel. This is the result of active restructuring of the cellular and noncellular components of the vessel wall. The total mass of the blood vessel may not increase. However, both the outer and inner diameters increase substantially, resulting in a reduced ratio of wall to lumen diameter. This form of remodeling is usually seen in large vessels. An example of this form of remodeling is vascular enlargement associated with a sustained high blood flow state. Yet another form of remodeling is a regression or downsizing of the blood vessel resulting from a frank reduction of the vascular mass and caliber. Here, both the outer and inner diameters are reduced with no change in the wall-to-lumen ratio. This process has been shown to occur in large and medium-sized arteries in response to a chronic reduction of blood flow.37 Finally, rarefaction of the microcirculation (a loss of capillary area), which is reported to occur in hypertension, may also be considered as a form of remodeling.38 An understanding of the mechanism of vascular remodeling may alter our therapeutic strategy in hypertension.

The spectrum of signals ranges from mechanical forces (shear stress and stretch) to vasoactive substances and inflammatory mediators. A number of reports have documented that shear stress may play an important role in regulating the size and structural characteristics of the vessel wall. Flow-induced vascular remodeling depends on the presence of an intact endothelium39 and is consistent with the concept of shear stress autoregulation, in which the vessel remodels itself such that the lumen is reshaped to maintain a given level of shear stress.39 Endothelial cells apparently sense shear stress via the activation of an inwardly rectifying potassium channel and hyperpolarization.40,41 Moreover, shear stress can activate phosphoinositol metabolism and may promote an increase in intracellular calcium.42,43 These events result in the release of local factors, such as nitric oxide, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), tissue plasminogen activator, and endothelin, that may participate in vascular remodeling.44-47

The blood vessel is also exposed to biaxial tension: tension in the plane of the endothelial and smooth muscle cells and compression along the radial plane. Recently, Harder48 reported that the autoregulatory increase in tone in response to stretch in the cerebral vasculature is caused by the release of an endothelium-dependent humoral factor or factors. The effect of stretch may also modulate vascular structure.49,50 The signal transduction mechanisms mediating the effects of stretch on vascular function are currently under study. One possible mechanism is suggested by the recent discovery by Lansman et al51 of a stretch-responsive nonspecific ion channel in bovine aortic endothelium.

In addition to hemodynamic factors, the endothelium responds to a variety of stimuli by specific receptor-coupled events. The calcium ion appears to play an important role in the signal transduction function of the endothelium. The changes in intracellular calcium by humoral factors are mediated via activation of phosphoinositol metabolism52-55 or receptor-coupled ion channels or agonist activation of potassium channels in endothelial cells.56,57

In response to hemodynamic forces, physical injury, or circulating factors, the cells in the vessel wall become activated to release growth modulators, cytokines, proteolytic enzymes, and matrix components, thereby participating in the process of vascular remodeling. Table 2 lists the autocrine-paracrine factors that regulate vascular cellular growth. These factors can be divided into growth promoters, growth inhibitors, or vasoactive substances with growth-regulatory properties. This classification is not rigid because it has been shown that a single factor may manifest multiple properties and perform several functions depending on the experimental condition.56-61

In addition to changes in cell migration and proliferation, matrix modulation is a key event in vascular remodeling. Expansion or contraction of extracellular matrix is a dynamic process that involves synthesis and/or degradation of matrix proteins and carbohydrates, including glucosaminoglycans, hyaluronic acid, collagen, elastin, and other components. Proteolysis and matrix degradation involve the activation and action of endogenous proteases such as tissue plasminogen activator, plasmin, elastase, collagenase, hyaluronidase, and heparinase.52-65 Endothelial cells also express a variety of adhesion molecules that regulate their adhesion to extracellular matrix and the organization of cell-cell junction.56,67

In hypertension, alterations in vascular structure are probably the consequence of increased pressure and flow, an imbalance of vasoactive substances, and endothelial dysfunction. Investigations of the pathobiology of hypertension and vascular remodeling are being
and contain low quantities of rough endoplasmic reticulum and a highly ordered contractile apparatus. Studies at the molecular level suggest that the most striking differences exist in the expression of contractile proteins and extracellular matrix. For example, myosin heavy chain exists at low levels in the normal adult vessel. Morphologically, neonatal smooth muscle cells exhibit a “synthetic” phenotype characterized by the presence of prominent rough endoplasmic reticulum, whereas adult smooth muscle cells exhibit a “contractile” phenotype and contain low quantities of rough endoplasmic reticulum and a highly ordered contractile apparatus. Studies at the molecular level suggest that the most striking differences exist in the expression of contractile proteins and extracellular matrix. For example, myosin heavy chain exists at low levels in the normal adult vessel.

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In the context of hypertension, the potential expression of the angiotensin system in the vessel wall during development and in neointimal hyperplasia is particularly interesting. ACE is expressed by the endothelium of adult blood vessels. It is barely detectable, if at all, in the adult tunica media or adventitia. However, in the neonate ACE is expressed in high concentration in the tunica media of the aorta. In the 1-day-old rat the tunica media of the aorta exhibits intensive ACE staining, and the neonatal markers such as fibronectin, osteopontin, and procollagen also exhibit high levels of expression in the neonate but not the adult vessel. In addition, growth factors and their receptors also exhibit differential expression.

In many instances, the response of the vascular smooth muscle cells (VSMCs) to injury involves a reexpression of this neonatal pattern of genetic expression. This has been examined in the greatest detail in the balloon-injured rat carotid artery, which develops neointimal hyperplasia. Many of the neonatal markers that are reexpressed in the growing VSMCs are constituents of the contractile apparatus, the paracrine growth factors, or the extracellular matrix and are presumably important to the growth characteristics of the cells.

The reexpression of developmentally regulated genes in the vessel wall in response to injury may have several implications toward the molecular mechanism of neointimal formation. The data are consistent with two distinct hypotheses. One hypothesis involves the dedifferentiation of the mature medial smooth muscle cells in response to injury. This dedifferentiated cell undergoes proliferation and migration to populate the neointima. The second hypothesis involves the presence within the normal media of an undifferentiated “stem” cell that responds to vascular injury with proliferation and migration. In either situation, some of the common biologically active substances synthesized in the developing blood vessel and the diseased adult blood vessel may play important roles in vascular cell growth, migration, and differentiation. Indeed, several growth factors (eg, PDGF, basic fibroblast growth factor, and TGF-β) have been shown to be expressed in the developing blood vessel and injured adult blood vessel.

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**Developmental Paradigms in Vascular Biology**

From studies in all areas of biology it is becoming increasingly apparent that the tissue or cellular response to injury or disease involves a recapitulation of an earlier developmental genetic program. In such diverse examples as skin wounding and pressure-overload cardiac hypertrophy, the response includes an induction of a neonatal or embryonic pattern of gene expression with a decrease in the adult pattern of expression.

Studies on the vasculature have shown that neonatal smooth muscle cells are phenotypically distinct from adult smooth muscle cells. During development, smooth muscle cells are involved in migration, proliferation, and synthesis of the extracellular matrix. The processes that occur at low levels in the normal adult vessel. Morphologically, neonatal smooth muscle cells exhibit a “synthetic” phenotype characterized by the presence of prominent rough endoplasmic reticulum, whereas adult smooth muscle cells exhibit a “contractile” phenotype and contain low quantities of rough endoplasmic reticulum and a highly ordered contractile apparatus. Studies at the molecular level suggest that the most striking differences exist in the expression of contractile proteins and extracellular matrix. For example, myosin heavy chain exists at low levels in the normal adult vessel.

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In Vivo Test of In Vitro Hypothesis: A Gene Transfer Approach

Many substances synthesized in the vasculature have been postulated to exert autocrine-paracrine actions on vascular function and/or structure (Table 2). However, definitive proof for their functions cannot be obtained because in vivo studies are limited by the multiplicity of coexisting variables, the difficulties in manipulating individual components, and the methodological limitations in studying the function of locally produced modulators in the absence of any contribution by the circulation. Cell culture and gene transfer technologies have provided us with the opportunity to study cellular responses to the manipulation of the individual components of a putative autocrine-paracrine mediator system (ie, by overexpression or inhibition). For example, transfection of an ACE expression vector into cultured VSMCs resulted in increased cellular ACE activity and stimulated DNA and RNA synthesis via increased Ang II production.99 These findings indicate that VSMCs contain components of the renin-angiotensin system and that cellular ACE is a rate-limiting step in Ang II generation in VSMCs in vitro. An in vivo experimental approach that can selectively manipulate vascular wall gene expression would be useful for furthering the understanding of the biology and pathobiology of the autocrine-paracrine system.
Recent progress in in vivo gene transfer technology may provide us with this possibility. The feasibility of transfecting blood vessels with foreign DNAs in vivo was shown previously with the use of retroviral vectors.96-98 As an alternative, direct physical transfer of genes into intact blood vessels in vivo has been reported with the use of cationic liposomes (Lipofectin) as the DNA carrier.99 Recently, the adenoviral vector transfer method has also been used successfully for gene transfer into the blood vessel.99,100 Several functional genes have been successfully transferred into endothelial cells and VSMCs in vivo. For example, the transfection of PDGF gene induced VSMC proliferation,101 whereas the transfection of fibroblast growth factor gene caused both angiogenesis as well as VSMC accumulation.102 These results emphasize the potential utility of the in vivo gene transfer method to dissect out the biologic role of locally generated vasomodulators within the vessel wall in vivo.

To further define the biologic role of locally generated vasoactive factors, we have recently used hemorrhaginating virus of Japan (HVJ)-liposome-mediated gene transfer103 into the vascular wall.104 This method yields high transfection efficiency (up to 30% of vessel wall cells may be transfected) without apparent toxicity. The usefulness of HVJ-liposome gene transfer for in vivo vascular biology studies has permitted us to examine the question of the autocrine-paracrine system in the vessel wall. The role of vascular ACE as a determinant of vessel tone and structure is a controversial subject in hypertension research. Given the difficulties of distinguishing between circulating and vascular ACE effects, traditional experimental approaches using pharmacologic tools have provided only indirect evidence of the potential importance of vascular ACE as a determinant of local Ang II generation. Using in vivo gene transfer, we tested the hypothesis that increased local expression of vascular ACE and production of Ang II are important determinants of vascular structure. Our data demonstrate that increased local expression of ACE within the vessel wall promotes autocrine-paracrine Ang II-mediated vascular hypertrophy in vivo.20 Thus, the use of in vivo gene transfer enabled us to address two important questions in hypertension and vascular research: (1) Can angiotensin directly mediate vascular hypertrophy independently of its blood pressure effect? and (2) is local tissue ACE important in regulating local vascular function and contributing to pathophysiology? These results have important implications in our understanding of the role of locally generated vasoactive substances in the process of vascular remodeling in hypertension.

As described above, in vivo gene transfer is suitable for studying vascular remodeling by local overexpression or inhibition of vasomodulators. In vivo gene transfer technology has the following advantages over conventional experimental approaches such as classic pharmacology: (1) The target gene can be transfected into a local segment of a blood vessel, thereby avoiding a systemic effect; (2) this transfected vascular segment can be compared with adjacent untransfected segments or with the contralateral control blood vessel, which are subject to the same hemodynamics and circulating humoral factors; and (3) the consequences of local overexpression within the physiological/pathophysiological range of the target gene may be studied. We anticipate that future studies will define the pathobiological role of autocrine-paracrine systems in the local regulation of vascular tone and structure.

Another tool for testing in vitro hypotheses in vivo is transgenic/gene targeting technology. This powerful technology is extremely useful for studies of gene functions in vivo. However, transgenic technology has several disadvantages: (1) It is time consuming and costly, (2) the effect of the overexpressed transgene is exerted throughout development, (3) it is impossible to target the transgenic expression to only a local segment of a blood vessel, and (4) it is difficult to exclude the potential contribution of the systemic effect of transgene expression. If knockout of the targeted gene is lethal, it is impossible to test the specific functions by transgenic or gene-targeting techniques. In those cases, the in vivo gene transfer approach may be ideal. Thus, the local gene transfer approach may be effective for studying the role of autocrine-paracrine mediators that are complementary to transgenic technology.

**Gene Therapy in Vascular Biology**

Local gene transfer technology also provides us with the opportunity to treat cardiovascular diseases. In several vascular diseases, no known effective therapy exists, eg, restenosis after angioplasty and accelerated transplant coronary vasculopathy. Because the molecular biology and pathophysiology of the vascular system is well understood,105 the time is ripe for the introduction of gene therapy to the management of vascular disorders. Table 3 summarizes the potential application of gene therapy for vascular diseases.

<table>
<thead>
<tr>
<th>TABLE 3. Gene Therapy for Vascular Disease</th>
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<tbody>
<tr>
<td><strong>Systemic gene therapy</strong></td>
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<tr>
<td>1. Atherosclerosis</td>
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<tr>
<td>2. Hypercoagulable states</td>
</tr>
<tr>
<td><strong>Local gene therapy</strong></td>
</tr>
<tr>
<td>1. Restenosis after angioplasty</td>
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<tr>
<td>2. Transplant rejection</td>
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<tr>
<td>3. Transplant vasculopathy</td>
</tr>
<tr>
<td>4. Angiogenesis</td>
</tr>
<tr>
<td>5. Thrombosis</td>
</tr>
<tr>
<td>6. Aortic aneurysms</td>
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Somatic gene therapy is the introduction of normal genes into the somatic cells of patients to correct an inherited or acquired disorder through the synthesis of specific gene products in vivo. In general, there are three methods of gene modification: gene replacement, gene correction, and gene augmentation. Although current in vivo methods for cardiovascular gene transfer are still limited by the lack of efficiency and potential toxicity,20 future advances may provide the opportunity to treat vascular diseases such as hypertension by manipulating vasodilator and growth inhibitory genes such as atrial natriuretic peptide or nitric oxide synthase.

Another attractive strategy involves an antigen approach, in which targeted genes are inactivated by
antisense oligonucleotides or plasmid. Such an approach can define the contribution of various factors to vascular pathobiology and may be used for therapy. To define the feasibility of an antigen approach for modulation of vascular structure in vivo, our initial studies have examined the determinants of VSMC growth in vivo using the rat carotid balloon-injury model. Neoinvasion after balloon injury involves a complex interaction between multiple growth factors that promote VSMC proliferation and migration, making it unlikely that selective inhibition of a particular growth factor will completely prevent lesion formation. However, growth factor–induced cell proliferation involves the sequential activation of intracellular proteins that promote cell cycle progression. Accordingly, we hypothesized that VSMC proliferation and lesion formation could be prevented by the blockade of genes regulating cell cycle progression—the final common pathway. Indeed, we have recently shown that in vivo gene transfer of antisense oligonucleotides against the cell cycle genes, proliferating cell nuclear antigen and cdc2 kinase, markedly inhibited VSMC proliferation and lesion formation after injury in vivo. Similarly, Simons et al reported the inhibition of neointimal formation by administering antisense oligonucleotides against c-myc. We speculate that continued development of these methodologies will facilitate the use of antisense oligonucleotide technology to further characterize the biologic role of gene products activated during the pathogenesis of hypertension as well as provide potential new therapeutic agents for use in human disease. Although the feasibility of gene therapy for hypertension remains a remote possibility, it is clear that this experimental technology will provide new insights into the pathogenesis of hypertension.

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