Vascular remodeling, used in the present discussion to represent any enduring change in the size and/or composition of an adult blood vessel, not only allows blood vessels to adapt and heal but also underlines the pathogenesis of major cardiovascular diseases, including atherosclerosis and restenosis. Physiological and pathological vascular remodeling entails degradation and reorganization of the extracellular matrix (ECM) scaffold of the vessel wall, explaining the recent interest in the potential participation of specialized enzymes, called matrix metalloproteinases (MMPs). The current discussion, which is part of a series of reviews examining various aspects of MMP participation in cardiovascular development, function, and pathology, will focus on what we perceive to be currently available pertinent informa-
tion, specific challenges, and yet unanswered questions that still limit our knowledge and thus the potential ability to use MMPs to control remodeling of blood vessels.

**MMPs: Agents of Change**

MMPs are an ever-expanding family of endopeptidases with common functional domains and mechanisms of action discovered because of their ability to degrade ECM components. MMP actions have been implicated in both physiological and pathological tissue reshaping, including organ development, wound healing, inflammation, and cancer. MMP activity is regulated at multiple levels: gene transcription and synthesis of inactive zymogens, posttranslational activation of zymogens, and interactions of secreted MMPs with tissue inhibitors of metalloproteinases (TIMPs). Enzymatic activation requires removal of their prodomain, which can occur through degradation by other proteases, such as plasmin, or cell-associated membrane-type MMPs (MT-MMPs). Alternatively, fully activated MMPs can arise through prodomain autolysis secondary to conformational changes that reveal the catalytic site. Such conformational changes also allow substrate lysis by pro-MMPs and are the basis for detection of both latent and activated MMPs in the presence of sodium dodecyl sulfate by zymography. Once activated, MMPs participate in a broad spectrum of physiological and pathological processes including, but not limited to, degradation of ECM components. Other important nonmatrix MMP substrates include molecules whose biological activity is regulated by MMP processing, such as TNF-α, growth factors and their receptors, plasminogen and its activators, and endothelin.

Because any lasting change in blood vessel structure entails remodeling of its matrix scaffold, MMP contribution has recently been questioned in relation to the main pathological vascular conditions characterized by wall remodeling, including atherosclerosis, development of restenotic lesions, arterial aneurysmal dilation, failure of vein grafts, and atherosclerotic plaque disruption. In vitro studies with cultured cells and histological observations of normal and diseased human and experimental blood vessels indicate that both vascular and inflammatory cells produce MMPs, although the spectra of MMPs secreted basally or in response to stimuli are distinctive. The major cellular constituents of normal blood vessels, human endothelial cells (ECs) and smooth muscle cells (SMCs), produce constitutively in vitro MMP-2, TIMP-1, and TIMP-2.

Immunocytochemical studies suggest that nondiseased human arteries and experimental animal arteries uniformly express, across the wall, MMP-2 and the inhibitory TIMP-1 and TIMP-2; however, no in situ enzymatic activity is detectable, suggesting tight control of MMP activity in the face of zymogen abundance. On the other hand, focally increased expression of several MMPs and presence of MMP activity were observed in diseased human arteries, and in association with arterial morphological changes in experimental models of atherosclerosis and restenosis, suggesting that MMPs enable blood vessel reshaping, including that associated with pathological conditions. Further evidence was obtained from in vitro studies of cultured vascular and inflammatory cells, which have tested the effect of stimuli characteristic for the environment of diseased vessels (Table).

**Major Stimuli of Vascular MMP Expression and Activity**

All acquired evidence indicates that the major drivers of vascular remodeling, hemodynamics, injury, inflammation, and oxidative stress, regulate MMP expression and activation. Although not clearly addressed in many studies that have investigated participation of MMPs in vascular remodeling, it is important to emphasize the distinction between regulation of MMP gene expression and that of their enzymatic activity, since the latter is likely to unleash the biological effects of MMPs.

By combining a low-flow state and balloon injury in rabbit carotid arteries, Bassiouney et al suggested that blood flow might be a more important regulator of arterial pro–MMP-2 expression than injury. Carotid artery flow cessation in a murine model resulted in an early significant upregulation of MMP-9 expression and expansive remodeling. Conversely, a nonselective MMP inhibitor inhibited the expansive remodeling at the site of rat arteriovenous fistulae. Elevation of transmural pressure in porcine arteries ex vivo induced the matrix-degrading activity of MMP-2 and MMP-9, suggesting that MMPs may also be involved in the early vascular remodeling associated with hypertension. Changes in the hemodynamic environment are thought to be of major importance in the failure of saphenous vein grafts. Investigation of potential MMP involvement has shown upregulation of MMP-2 and MMP-9 production after transposition of porcine saphenous veins in the carotid artery position. Ex vivo comparison of human saphenous vein grafts in simulated arterial versus venous conditions indicated that arterial conditions stimulate MMP expression and activation, likely via control of the vessel wall’s redox state.

Several other recent studies suggest that MMP-mediated vascular remodeling in response to hemodynamic conditions could be modulated by the interplay between reactive nitrogen and oxygen species, which can lead to local oxidative stress. The role of nitric oxide (NO) in the shear-induced remodeling response was indicated by the lack of compensatory arterial remodeling in response to increased flow in endothelial nitric oxide synthase (ecNOS)-null mice. NO breakdown, together with accumulation of collagen, was considered responsible for constrictive remodeling of rabbit femoral arteries after balloon injury. Studies of flow-induced remodeling of rabbit arteriovenous fistulae suggested that the effect of NO might be exerted via modulation of MMP expression. In vitro ecNOS gene transfer to SMCs was shown to reduce MMP-2 and MMP-9 expression and impair their migration. However, it has become apparent that the biological effects of NO are modified in the presence of other reactive species generated in diseased vessels by activated vascular cells and infiltrating inflammatory cells. For instance, simultaneous production of NO and superoxide, generates peroxynitrite, found to activate latent MMPs, and degrade TIMP-1. Therefore, whereas under normal conditions NO production in healthy vessels may help keep MMP expression in check, in diseased vessels, products of NO
secondary reactions may tip the MMP/TIMP balance in favor of matrix degradation. Other reactive species such as hydrogen peroxide, which can be generated from superoxide through the action of dismutases, can also modulate the activity of MMPs.52

Inflammatory cells are an important source of MMPs and other proteases, such as cathepsins, which degrade vascular matrix. In addition, activated macrophages secrete cytokines that upregulate MMP gene expression in vascular cells,11,53 Intracellular accumulation of lipid, characteristic of macrophages residing in atherosclerotic plaques, or in vitro incubation with oxidized lipoproteins, increases MMP expression in macrophages,17,58 as well as vascular cells.22,44 Presence of foam cell macrophages further enhances the oxidative stress through increased production of reactive oxygen species (ROS), which among other actions can trigger the activation of latent MMP zymogens stored in the vessel wall.32 Thus, macrophage foam cells resident in atheroma have the complete arsenal required to degrade matrix. All these actions facilitate the proteolytic degradation of matrix and may be related to the weakening of plaques with high content of foam cell macrophages.54 Focal degradation of the fibrous cap collagen by MMPs produced by foam cell macrophages was demonstrated ex vivo in human atheroma50 and was associated with in vivo rupture of an experimental model of atherosclerotic lesions developed in rabbit.25 Similar ROS-dependent activation of MMPs has been reported in connection with degradation of mast cells in the shoulder region of atherosclerotic plaques23 and would occur in other circumstances leading to release of ROS within the vessel wall, thus enabling degradation of matrix and consequently vascular remodeling. Oxidative stress-driven remodeling may also explain the correlation between hypercholesterolemia and expansive remodeling of coronary arteries in patients with myocardial ischemia59 and the prevalence of coronary ectasia in the setting of heterozygous familial hypercholesterolemia.56 On the other hand, scavenging of ROS50 and lipid lowering24 have decreased MMP expression in experimental atheroma. Interestingly, HMG-CoA reductase inhibitors, a widely prescribed class of lipid-lowering agents, decrease MMP expression in macrophages57 as well as vascular cells.58

MMPs and Vascular Remodeling in Atherosclerosis

The growth of atherosclerotic plaque occurs through structural changes that lead to accumulation of cells, ECM, and lipids within the intimal layer of the diseased artery. Although the exact mechanisms that lead to an increased number of intimal SMCs in atherosclerotic lesions remain largely unknown, the contribution of early migration and proliferation of medial SMCs has been suggested.59 Increased MMP expression and activity were associated with development of neointimal arterial lesions and SMC migration after arterial balloon injury in experimental models, whereas MMP inhibition decreases SMC migration in vitro and in situ.34,35,60,61

Another major contributor to the growth of atherosclerotic lesions is through the recruitment of circulating inflammatory cells,62 mediated via interactions with adhesion molecules expressed by the activated endothelium.63 The mechanisms allowing for the subsequent infiltration of leukocytes through the endothelial layer and its associated basement membrane after the adhesion event remain largely unknown. Recent experiments suggest that MMP action may facilitate this step. Direct interaction of monocytes with a paraformaldehyde-fixed monolayer of human ECs was shown to increase monocyte MMP-9 production severalfold,64 but the mechanism was not explored. Cellular interaction in vitro between T lymphocytes and EC monolayers was shown to trigger T-cell secretion of MMP-2, the other basement membrane-degrading MMP.65 Release was dependent on the expression of VCAM-1 by the ECs. Surprisingly, the effect of cell-cell interaction on endothelial MMPs was not assessed in either study. MMP degradation of EC basement membrane during diapedesis of inflammatory cells could contribute to a decreased endothelial barrier function66 with increased influx of plasma proteins, including lipoproteins. Once inside the vessel wall, infiltrating cells interact with ECM, oxidized lipids, and with each other. All of these interactions have been shown to increase production of MMPs in macrophages,38,67,68 As mentioned, macrophages also provide stimuli for MMP production in neighboring cells and mechanisms for activation of secreted MMP zymogens.69 This increased MMP activity in developing atherosclerotic lesions may facilitate further structural changes and enable their growth (Figure 1).

Clinically significant atherosclerosis has been associated with obvious morphological changes of diseased arteries. Interestingly, these changes span the whole spectrum to include progressive flow-limiting stenosis, resulting in claudication or stable angina, as well as aneurysmal dilation, resulting in dissection or rupture. Recent basic research and advances in clinical imaging have underscored the realization that while atheroma develops within the intimal layer, the whole arterial wall undergoes major reshaping. The lumen size, which is the major functional parameter, is ultimately determined not only by the magnitude of the intimal lesion but also by the overall size change of the remodeling arterial wall. Geometrical vascular remodeling can be expansive, also known as outward or positive remodeling, or constrictive, also known as inward or negative remodeling. These later considerations shifted the classic emphasis away from the burden of the intimal lesion, consequently changing our current appreciation of pathological determinants of vascular remodeling in general and of atherosclerosis in particular. The current concept of atherosclerosis, which places emphasis on the remodeling of the arterial wall, provides a framework for understanding how, through weakening and destabilization, angiographically undetectable moderate lesions could become culprits for acute coronary syndromes. It is our belief that acute cardiovascular events in fact represent a late stage of vascular remodeling.54 The action of MMPs has been studied in relation to formation of intimal lesion and overall geometrical remodeling, as these both require sustained changes in the structure and dimensions of the arterial wall (Figure 2).
## Vascular MMPs

<table>
<thead>
<tr>
<th>MMP</th>
<th>Species</th>
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<th>Location</th>
<th>Stimulus</th>
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<td>Rabbit</td>
<td>Macrophage foam cell</td>
<td>In vitro</td>
<td>ROS</td>
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Outward Geometrical Remodeling: Too Much of a Good Thing May Be Bad

Outward remodeling delays the development of flow-limiting stenosis by preserving the lumen.70,71 The trigger for outward remodeling is thought to be the physiological tendency of blood vessels to optimize shear stress and wall tension.72 Because such expansive remodeling of the arterial wall likely requires releasing the constraints imposed by the structural scaffold of ECM, it is plausible to suspect that the action of MMPs is involved. Pasterkamp et al73 observed more immunopositive MMP-2 and MMP-9 and more MMP-2 activity in plaques of expansively remodeled segments compared with constrictively remodeled segments of human coronary arteries. Experimental overexpression of MMP-9 in rat SMCs enlarged the circumference of arteries seeded with such cells.74 On the other hand, nonselective MMP inhibition was found to diminish expansive arterial remodeling of rat arteriovenous fistulae.46 Treatment of LDL receptor–null mice with another nonspecific MMP inhibitor has been shown to retard expansive aortic remodeling.75

Although outward remodeling is initially beneficial by preserving the lumen, recent evidence suggests it may ultimately increase the propensity for plaque destabilization and rupture. Angioscopic and intravascular ultrasound (IVUS) studies of coronary artery lesions associated with unstable angina were associated with larger lesions and outward remodeling compared with those of stable angina, which were more fibrous and calcified.76,77 Previously identified markers

<table>
<thead>
<tr>
<th>MMP</th>
<th>Species</th>
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<td>EC</td>
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<td>Plasmin</td>
<td>36</td>
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</table>

Figure 1. Cells within the vessel wall produce and secrete MMPs. Expression of various latent (pro-) MMPs is increased in atherosclerotic lesions. The spectrum of MMPs is diversified through the presence of inflammatory cells, stimulation by soluble factors, cell-cell, and cell-matrix interactions. Degradation of matrix by activated MMPs, detectable in vessels undergoing remodeling, is thought to facilitate cell migration and general reorganization of vascular tissue. Ultimately, MMPs are thought to weaken the arterial wall, thus contributing to destabilization and rupture of atherosclerotic plaques.
of plaque instability, rich inflammatory infiltrate and decreased collagen and SMCs in the caps and shoulders of atheroma,78–80 have been more recently also associated with outward vessel remodeling.81 The postmortem examination of human coronary arteries revealed increased immunostaining of MMP-2 and MMP-9, but not MMP-1, and elevated MMP-2 activity in the plaques of expansively remodeled segments.73 Thus, the increased matrix degradation that enables outward remodeling may eventually result in the weakening of the vessel wall.

Aneurysmal arterial dilation may represent an extreme form of outward remodeling. Increased MMP-2 and MMP-9 expression was detected in human abdominal aortic aneurysms (AAAs).82,83 Medial SMCs isolated from AAA tissue seem to produce significantly higher levels of MMP-2 and MMP-9 in vitro than cells obtained from control arterial tissues.27 However, the histological feature most clearly associated with enlarging human AAA diameter is a higher density of mural inflammation, composed primarily of macrophages.84 Increased MMP-9 expression may account for the propensity of AAAs to continue to expand.85 Local TIMP-1 overexpression prevented aneurysmal degeneration and rupture in a rat model of aneurysm.86 Experimental models of aneurysmal destruction of arteries in genetically deficient mice showed protection in MMP-9–null animals,87 confirming an important role for MMP-9. These experiments also suggested that the protective effect of urokinase-plasminogen activator (u-PA) deficiency against medial destruction and aneurysm formation is exerted indirectly by means of reduced activation of pro-MMPs by plasmin.36

The outward or positive remodeling preserves the lumen, however, in the process may decrease the mechanical strength of the arterial wall and thus may not be very positive after all.

**Plaque Instability**

The demise of atherosclerotic plaque occurs through structural disruption of the arterial wall, which triggers thrombosis, the cause of occlusion and the majority of acute vascular events.88 Plaque disruption takes one of two forms, frank rupture and superficial erosion.89,90 Rupture is associated with fracture of the fibrous cap with exposure of the prothrombotic core.90 The discovery of strong local MMP overexpression and in situ matrix-degrading activity in the vulnerable shoulders of human atheroma,12 seemingly overcoming inhibition by ubiquitously expressed TIMPs, later found to coincide with areas subjected to the highest mechanical stress,91 has provided a potential mechanistic insight into the process of plaque destabilization through matrix weakening by MMPs, especially in the vulnerable shoulders.94 Analysis of human coronary atherectomy specimens revealed uniformly active synthesis of MMP-9 by macrophages and SMCs in lesions of patients with unstable versus stable angina,14 suggesting the role of this specific MMP in acute syndromes. Peripheral blood levels of MMP-2 and MMP-926 may be increased in patients with acute coronary syndrome, raising the interesting question of the possibility to develop noninvasive tests for detection of plaque vulnerability.

Resident macrophage-derived foam cells, characteristic of unstable plaques, have been identified as a major source of MMPs, including MMP-1, MMP-2, MMP-3, MMP-7, and MMP-associated activity in human and experimental atherosclerotic lesions.12,17,40 The mechanism responsible for locally increased expression and activation of macrophage-derived MMPs, which may enable arterial remodeling and precipitate plaque destabilization, is likely related to oxidative stress.32 The capacity of human monocyte-derived macrophages to induce collagen breakdown in the fibrous caps of atheromas via release of MMPs was demonstrated ex vivo.20 Using a cleavage-specific antibody, in situ–degraded collagen was found to colocalize with MMP-1– and MMP-13–positive macrophages in atheromatous human carotid arteries.21

Alternative or complementary systems for activation of latent MMPs in atherosclerotic plaques have been suggested. Thrombin has been shown to proteolytically activate purified pro–MMP-2 in vitro and thus could provide cell-independent MMP
activation at sites of vascular injury. In complicated atherosclerotic plaques, thrombin could promote plaque instability in episodes of intraplaque hemorrhage or superimposed plaque thrombosis by increasing the local matrix-degrading activity of MMPs. The mutually activating MMP/thrombin system may serve as an important positive-feedback loop in acute coronary syndrome. As acute plaque disruption leads to local thrombin production at the site of vascular injury, this may facilitate proteolytic activation of MMP-2, shown to be able to mediate platelet aggregation, thus further generation of thrombin and, respectively, more MMP-2 activation. Pericellular activation of pro–MMP-2 can be achieved by MT-MMPs, expressed by vascular ECs and SMCs in response to cytokines and oxidized lipoproteins. The plasminogen cascade represents another proteolytic-activating mechanism of MMP zymogens. Its contribution to the development of experimental neointimal lesions after injury and to aortic medial destruction was demonstrated in u-PA and plasminogen activator inhibitor (PAI)-1–null mice and apolipoprotein E (ApoE)–null mice, respectively.

**Arterial Stenosis**

A common occurrence after the treatment of coronary and peripheral atherosclerosis by balloon angioplasty, restenosis is a result of the concomitant contribution of intimal hyperplasia as well as constrictive remodeling. Histological and IVUS studies have suggested that the degree of luminal narrowing is more dependent on the direction of geometrical remodeling. In addition, serial IVUS studies revealed that constrictive remodeling of human coronary arteries after angioplasty and atherectomy was the most important determinant of restenosis and of posttransplant vasculopathy.

The reaction of various components of the vessel wall to direct vascular injury by balloon angioplasty has been investigated in many experimental models, including the rat, pig, primates, and mouse arteries. This shares major features with the process of wound healing, including deposition of collagen and tissue contraction. The remodeling of matrix is a result of the interplay between increased degradation early after injury and subsequent matrix accumulation and contraction. Such a temporal sequence was suggested by studies of arterial remodeling after balloon injury in the rabbit, which showed a delay between the immediate increase in procollagen mRNA expression and a detectable increase in vessel mural collagen content. This pattern may be due to a post–balloon injury peak in MMP expression and activity, reported in numerous studies. Studying the effects of angioplasty in rabbits with previously developed atherosclerotic lesions, Coats et al reported that an increase in gelatinase activity, concurrent with decreased collagen content, was associated with restenosis, further supporting a role for gelatinases in intimal thickening.

The contribution of SMC migration and thus the need for degradation of the internal elastic lamina to remain to be demonstrated in pathogenesis of human lesions. This is likely necessary in experimental models whose normal arteries do not initially contain intimal SMCs, such as the rat and mouse carotid arteries. Administration of a nonselective MMP inhibitor reduced SMC migration and neointimal thickening in the rat carotid injury model, supporting MMP participation in the breakdown of vascular matrix and especially of the internal elastic lamina allowing migration of SMCs from outer layers. Similarly, synthetic MMP inhibitors and antibodies raised against MMPs dramatically reduce in vitro migration of rat SMCs through a reconstituted basement membrane. Conversely, overexpression of MMP-9 has been shown to enhance migration of rat SMCs in a collagen invasion assay. Proteolytic activators of latent MMPs, plasmin, and thrombin, may cooperate to enhance SMC migration. Inactivation of these proteases through use of specific antibodies inhibited in vitro migration of primate aortic SMCs, whereas genetic deficiency inhibited in vivo SMC migration and neointima formation in mice. The discovery that use of either MMP or serine elastase inhibitors reverses the progressive thickening of rat pulmonary artery in organ culture also supports cooperation between MMPs and serine proteases in processes associated with vascular remodeling.

The migratory advantage of adventitial fibroblasts compared with medial SMCs of porcine coronary artery has been attributed to characteristic transmural variations in the balance between MMPs and TIMPs. MMPs may also play a role in SMC proliferation, as suggested by experiments where MMP inhibitors diminished rabbit vascular SMC proliferation in vitro. The overexpression of various TIMPs in rat SMCs has been shown to result in multiple divergent effects including inhibition of SMC proliferation and migration, induction of SMC apoptosis, decreased intimal hyperplasia, and increased accumulation of matrix after arterial balloon injury.

**MMPs and Heterogeneity of the Remodeling Response**

The remodeling response of blood vessels has been previously shown to depend on a variety of endogenous and environmental factors. These can vary for instance from vessel to vessel, as constrictive or inadequate expansive remodeling seems common in iliofemoral arteries, but not in renal arteries, varies with age and gender, and is modulated by known cardiovascular risk factors. Angiographic as well as IVUS data have suggested that negative and inadequate positive coronary artery remodeling are more common in individuals who smoke and in individuals with insulin-dependent diabetes compared with non–insulin-dependent diabetes but less frequent in individuals with hypercholesterolemia. Recent advances in comparative genetic analyses of normal and diseased tissue can detect the presence of unique genes or variations of common ones. As these become more reproducible and widely available, such techniques are expected to add new dimensions to the classical pathological investigative characterization of features associated with the vulnerable or ruptured plaque phenotypes. Identified potential molecular targets that will be further validated by other techniques may become useful markers for early diagnostics or targets for tailored treatment of plaque vulnerability.

An emerging concept is that variations in MMP expression and activity contribute to the heterogeneity in the presentation and natural history of atherosclerosis. Recent observations
suggest genetic diversity that affects expression of various members of the MMP family may contribute to progression of cardiovascular disease. A common polymorphism in the promoter region of the human MMP-3 gene causing reduced enzyme expression has been associated with a more rapid progression of angiographically detectable lesions in patients with documented coronary artery disease who were homozygous for the allele. In a more recent study, carriers of this genotype were found to have increased common carotid wall thickness, enlarged lumen, and local reduction of wall shear stress, which could predispose to formation of atherosclerotic plaques. Interestingly, these observations suggest that decreased expression of MMP-3 makes matters worse, whereas postmortem observations of advanced human lesions suggest that increased focal expression and activity of MMP-3, and of MMPs in general, increase plaque vulnerability and contribute to acute events, underscoring the complexity of MMP actions. In accord with these observations, heterozygosity or homozygosity for a common polymorphism in the MMP-9 promoter, which leads to increased MMP-9 transcription, has been associated with an increased likelihood of detecting triple-vessel disease on angiography in patients with known coronary artery disease. Further complexity arises through the presence of other risk factors that can add to, or even exacerbate, effects of some of the MMP genetic polymorphisms on remodeling before, or in response to interventions. For instance, a common functional polymorphism within the MMP-12 promoter was associated with smaller luminal diameter coronary artery disease in patients with diabetes.

**Why Didn’t We Figure It Out Yet? Are They Good, Are They Bad, and Are They Responsible for the Ugly?**

The physiological activity of MMPs must be tightly regulated in normal arteries considering that the MMP family is capable of degrading all the individual components of blood vessel ECM. An ever-increasing fund of experimental as well as clinical data illustrates the key role of MMPs in many of the processes that control vascular remodeling and especially formation and progression of atherosclerotic plaques. The net effect of the various triggers shown to increase MMP activity in the setting of atherosclerosis and vascular remodeling is an imbalance of the MMP:TIMP ratio in favor of ECM degradation. Therefore, it is conceivable that modulation of MMP activity or the MMP:TIMP balance may be useful in the management and prevention of atherosclerosis. Such approaches may hold great promise for the therapeutic management of clinical cardiovascular conditions, including acute coronary syndrome.

Recent efforts focused on finding ways to control the action of vascular MMPs through the use of nonspecific inhibitors or of natural inhibitors. The use of various nonselective MMP inhibitors to modify the natural progression of arterial restenosis after experimental balloon injury has produced mixed results. In the rat carotid artery, administration of an MMP inhibitor resulted in a 97% reduction in the number of SMCs migrating into the intima after balloon angioplasty; however, medial SMCs in treated animals reportedly underwent increased replication and eventually caught up with the untreated control lesion. Yet others have found that administration of a nonselective MMP inhibitor decreased constrictive arterial remodeling without reduction of neointimal formation in a porcine balloon injury model. Treatment of LDL receptor–null mice with yet another nonselective MMP inhibitor has been shown to retard expansive aortic remodeling. Thus, decreased arterial remodeling through MMP inhibition could be interpreted as beneficial in the setting of aneurysmal dilation, however equivocal in restenosis where little impact on lumen preservation was noted due to persistent neointimal reaction despite inhibition of constrictive remodeling.

Unfortunately, because of the current absence of selective MMP inhibitors, experiments have provided little insight into the role of individual MMPs, which may prove essential especially in the complicated local milieu of atherosclerotic lesions, which contains many potential substrates whose biological activity can be modified by MMPs. Experimental genetic manipulation of expression of individual MMPs or TIMPs may represent a more promising way to understand the specific activities of selective members of the large family of MMPs in isolation. Several recent studies using genetically modified animals, tissues, and cells have provided support for participation of MMP in vascular remodeling. For instance, it has been reported that MMP-9–deficient mice are resistant to experimentally induced abdominal aortic aneurysmal dilation. Recently, transgenic mice modified to express human MMP-1 in macrophages were crossed into the ApoE-null background and fed an atherogenic diet. Interestingly, the transgenic mice demonstrated markedly diminished lesion formation compared with controls. Effects of plasmin inactivation in genetically deficient mice have been correlated to decreased expression and activation of several MMPs. Adenoviral transfection of human saphenous vein organ culture with TMP-1 and TIMP-2 has been shown to inhibit MMP-2 and MMP-9 gelatinolytic activity and reduce neointimal thickening without inhibiting MMP-2 and MMP-9 production or SMC proliferation. Overexpression of TIMPs in rat vascular SMCs has resulted in a variety of divergent MMP-dependent and -independent effects.

MMPs govern processes essential for the remodeling of blood vessels. Soluble factors, cell-cell, and cell-matrix interactions finely tune MMP expression and activation spatially and temporally. Although essential for the development and normal turnover of blood vessels, and beneficial for their adaptation and repair, the action of MMPs can evade normal control and thus push remodeling over the edge. A thorough understanding of the control and consequences of MMP actions may provide new ways to manipulate vascular remodeling. To complicate matters further, new insights obtained from recent studies with MMP inhibitors and genetic manipulation suggest that depending on the setting and timing, modulation of specific MMP activities may be considered beneficial or detrimental for vascular remodeling.

The burden of proof in demonstrating a direct relationship between the action of MMPs and various aspects of vascular remodeling relies on development of specific inhibitors, appropriate animal models, and diagnostic tools. Especially
attractive is the hypothesis that control of MMPs could allow the stabilization of atherosclerotic plaques, thus preventing the occurrence of their clinical consequences. However, the proof of a causal connection between plaque rupture and matrix weakening by MMPs, or of other destabilizing mechanisms for that matter, remains elusive. 131 Appropriate experimental models that could test mechanisms of plaque rupture are still lacking, in spite of recent reports of occurrence of spontaneous plaque rupture in mice. 132 New technologies that may identify genes uniquely associated with various types of pathological remodeling still present challenges, but also a lot of promise. 120 The advent of better clinical imaging should be able to soon create pictures detailed enough to identify all parameters currently thought to define vascular remodeling and indicate potential changes with treatment. Then, the day when all the tools will be in place, we should be able to shift vascular remodeling one way or the other. We better be ready to decide when and what is good or bad in order to avoid the ugly.

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