Cyclic strain-mediated matrix metalloproteinase regulation within the vascular endothelium: a force to be reckoned with

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Cyclic strain-mediated matrix metalloproteinase regulation within the vascular endothelium: a force to be reckoned with. Am J Physiol Heart Circ Physiol 292: H28–H42, 2007. First published September 1, 2006; doi:10.1152/ajpheart.00304.2006.—The vascular endothelium is a dynamic cellular interface between the vessel wall and the bloodstream, where it regulates the physiological effects of humoral and biomechanical stimuli on vessel tone and remodeling. With respect to the latter hemodynamic stimulus, the endothelium is chronically exposed to mechanical forces in the form of cyclic circumferential strain, resulting from the pulsatile nature of blood flow, and shear stress. Both forces can profoundly modulate endothelial cell (EC) metabolism and function and, under normal physiological conditions, impart an atheroprotective effect that disfavors pathological remodeling of the vessel wall. Moreover, disruption of normal hemodynamic loading can be either causative of or contributory to vascular diseases such as atherosclerosis. EC-matrix interactions are a critical determinant of how the vascular endothelium responds to these forces and unquestionably utilizes matrix metalloproteinases (MMPs), enzymes capable of degrading basement membrane and interstitial matrix molecules, to facilitate force-mediated changes in vascular cell fate. In view of the growing importance of blood flow patterns and mechanotransduction to vascular health and pathophysiology, and considering the potential value of MMPs as therapeutic targets, a timely review of our collective understanding of MMP mechanoregulation and its impact on the vascular endothelium is warranted. More specifically, this review primarily summarizes our current knowledge of how cyclic strain regulates MMP expression and activation within the vascular endothelium and subsequently endeavors to address the direct and indirect consequences of this on vascular EC fate. Possible relevance of these phenomena to vascular endothelial dysfunction and pathological remodeling are also addressed.

endothelial cells; smooth muscle; shear stress

MECHANICAL OR HEMODYNAMIC forces associated with blood flow play a pivotal role in the physiological control of vascular tone, remodeling, and the initiation and progression of vascular pathologies. Disruption of normal hemodynamic loading can be either causative of or contributory to several life-threatening diseases including hypertension (HT), intimal hyperplasia (IH), and atherosclerosis. With respect to the latter, for example, a variety of systemic risk factors (e.g., smoking, hyperlipidemia, genetic factors) have been found to promote atherosclerosis. Although these factors affect blood vessels equally, atherosclerotic lesions typically develop at predictable locations (e.g., branch points, bifurcations, sites of injury and infection), suggesting that the development of clinically significant plaques involves a complex interplay between vascular anatomy, vascular biology, and hemodynamic forces. One such force is cyclic circumferential strain caused by a transmural force acting perpendicularly to the vessel wall (i.e., a tensile component of blood pressure), leading to outward stretching of both vascular endothelial cells (ECs) and smooth muscle cells (SMCs) and causing rhythmic distension of the arterial wall (in this context, cyclic refers to frequency of pulses or circumferential distensions per second). Equally important is fluid shear stress, the frictional force generated as blood drags against vascular ECs (i.e., a frictional component of blood flow velocity) (Fig. 1) (80, 146). Both forces can profoundly modulate vascular cell processes and, under normal physiological conditions, impart an atheroprotective effect that disfavors pathological changes in vessel wall structure.

Essential to cell survival and function is the ability to interact properly with the immediate environment. This environment includes other cells and the meshwork of specialized proteoglycans and glycoproteins in which they are assembled, collectively referred to as the extracellular matrix (ECM) (18). In addition to acting as a support scaffold for cells within tissues, the ECM directly participates in wound repair,
The vascular endothelial monolayer or endothelium is a dynamic cellular interface between the vessel wall and the bloodstream. In addition to regulating the physiological effects mediating cellular proliferation, migration, and apoptosis. In this regard, cell-matrix interactions invariably involve degradation/modification of matrix proteins via matrix metalloproteinases (MMPs), a diverse family of mechanosensitive zinc-dependent proteases that degrade ECM components (e.g., collagen, laminin, and fibronectin) and nonmatrix substrates (e.g., growth factors and cell surface receptors) (99). Several studies have demonstrated that hemodynamic forces can modulate MMP expression and activity in different vascular cell types, with consequences for vascular cell fates (152–155). Moreover, published findings also confirm force-dependent modulation of ECM protein expression (e.g., tenasin-C and collagen) (18). Thus the production, composition, and MMP-dependent modification of the ECM is a central feature of how vascular cells respond to hemodynamic stimuli.

In view of the growing importance of blood flow patterns and mechanotransduction to vascular health and pathophysiology, and considering the potential value of MMPs as therapeutic targets, a timely review of our collective knowledge of MMP mechanoregulation and its impact on vascular cell fate is warranted. Considering the broad scope of this subject, we have decided to sharpen the focus of this article by restricting our review to cyclic circumferential strain and specifically its regulation of MMP expression and activation within the vascular endothelium (although occasional references to both SMCs and shear stress are also made within an appropriate context). After an introduction to the vascular endothelium and MMPs, this review presents a detailed examination of our current knowledge of how cyclic strain regulates vascular endothelial MMP expression and activation, from transcriptional to posttranslational levels. As a logical extension to this, we then endeavor to examine how cyclic strain, by engaging cellular machinery to modulate active MMP levels, directly and indirectly impacts on vascular EC fate. Finally, the relevance of these phenomena is discussed with respect to vascular endothelial dysfunction and pathological remodeling.

Cyclic Strain and the Vascular Endothelium

The vascular endothelial monolayer or endothelium is a dynamic cellular interface between the vessel wall and the bloodstream. In addition to regulating the physiological effects of humoral and mechanical stimuli on vessel tone and remodeling, the endothelium participates in immune and inflammatory reactions and presents a nonthrombogenic surface for blood flow (127). Moreover, the vascular endothelium constitutes a highly effective fluid and solute barrier (2). Of central importance among the physiological stimuli that impact on the endothelium are blood flow-associated forces such as cyclic strain (and shear stress). In vitro, the effects of cyclic strain on vascular ECs have typically been investigated according to the method of Banes et al. (7). Essentially, ECs are cultured on ligand-coated silicon membranes, with subsequent membrane deformation by microprocessor-controlled vacuum to produce physiologically relevant levels of stretch (normally 0–15%, uniaxial or equibiaxial) (22, 152–154). Numerous studies have also investigated the effects of cyclic strain on aortic ECs ex vivo (81, 133). Both models reveal that cyclic strain has a profound impact on endothelial metabolism and can induce qualitative and quantitative changes in gene expression leading to changes in cell fate, with consequences for endothelial phenotype and vessel wall homeostasis (17, 111, 146). In addition to affecting the expression and/or activation of numerous signaling molecules associated with mechanotransduction, cyclic strain has been shown to regulate the expression and/or activation of several classes of effector genes (and gene products) in vascular ECs, including those regulating J) vessel diameter; NO, nitric oxide synthase (NOS), cyclooxygenase-2 (COX-2), endothelin (ET)-1, and thimet oligopeptidase (16, 20, 22, 74); 2) proliferation: platelet-derived growth factor (PDGF) and vascular endothelial growth factor (140, 169); 3) migration/angiogenesis: Arg-Gly-Asp (RGD)-dependent integrins, urokinase-type plasminogen activator (uPA), plasminogen activator inhibitor (PAI)-1, monocyte chemotactic protein (MCP)-1, MMP-2, MMP-9, and membrane type 1 MMP (MT1-MMP, MMP-14) (150, 152–155, 162, 164); and 4) cell-cell communication/barrier function: intercellular adhesion molecule (ICAM)-1, zonula occludens (ZO)-1, and occludin (21, 117).

Vascular ECs sense and respond to cyclic strain both morphologically and phenotypically. The influence of cyclic strain on ECs is visually apparent as early as 15 min after strain with the formation of actin stress fibers and morphological alignment of cells perpendicular to the force vector (58). Alignment is subsequently followed by phenotypic or cell fate changes. Physiological levels of cyclic strain on aortic ECs, for example, have been shown to increase both migration (154) and proliferation (60, 84), while concomitantly reducing apoptosis (51, 87), cell fates that are discussed below. In addition, the initiation and progression of angiogenesis, a complex physiological
process leading to the growth of new blood vessels from existing capillaries, has been shown to depend primarily on the complex interplay of vascular endothelial responses to a collective of factors including hemodynamic forces, metabolic status (i.e., injury, oxidative stress, inflammation), and growth factors (67, 154, 169). It should be noted, however, that the effects of cyclic strain on vascular endothelial phenotype may vary as a function of vascular bed as well as cell type (e.g., macro- vs. microvascular), a finding eloquently demonstrated in the work of Iba et al. (60), who show that cyclic strain may differentially affect EC morphology and proliferation depending on the vascular bed (i.e., aortic vs. vena cava vs. pulmonary).

Matrix Metalloproteinases

MMPs are a growing multigene family presently comprising 25 secreted and cell surface enzymes grouped into 6 subfamilies (Table 1). These include 25 vertebrate and 22 human homologs in addition to a number of nonvertebrate MMPs (99). MMPs are identified by the following shared characteristics. 1) In addition to a zinc-binding motif and methionine turn, they share added stretches of common amino acid sequences. 2) They exist as either a secreted or a transmembrane proenzyme, which requires activation. 3) A second metal cofactor (other than zinc) is often required for catalysis. 4) They are sensitive to inhibition by tissue inhibitors of metalloproteinases (TIMPs) (99).

MMPs are typically secreted as latent enzymes, which can be activated by reactive oxygen species (ROS), low pH, exposure to thiol-modifying reagents, and indeed by other proteinases (including other MMPs) (99). Activation typically requires removal of the cysteine switch, which blocks the catalytic site by a zinc-cysteine interaction. MMP expression is highly tissue specific and is tightly regulated at the transcriptional, posttranscriptional, and posttranslational levels. Moreover, for either their normal or pathological functions, MMPs must be present in the correct cell type and pericellular location (138).

The involvement of MMPs in cyclic strain-mediated regulation of EC phenotype has been the subject of much investigation. The following sections therefore present a detailed examination of our current knowledge of how cyclic strain regulates vascular endothelial MMP expression and activation, from transcriptional to posttranscriptional levels. This is followed by an examination of how cyclic strain-mediated regulation of MMP levels influences vascular EC (and SMC) fates and concludes with a discussion of how these phenomena are

### Table 1. Classification of matrix metalloproteinases

<table>
<thead>
<tr>
<th>Category</th>
<th>MMP Name</th>
<th>Substrate(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenases</td>
<td>MMP-1</td>
<td>Collagens (I, II, III, VII, VIII, and X), gelatin, aggrecan, L-selectin, IL-1β, proteoglycans, entactin, ovostatin, MMP-2, MMP-9</td>
</tr>
<tr>
<td>Collagenase 1</td>
<td>MMP-8</td>
<td>Collagens (I, II, III, V, VII, VIII, and X), gelatin, aggrecan, fibronectin</td>
</tr>
<tr>
<td>Collagenase 3</td>
<td>MMP-13</td>
<td>Collagens (I, II, III, IV, IX, X, and XIV), gelatin, plasminogen, aggrecan, perlecan, fibronectin, osteonectin, MMP-9</td>
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<tr>
<td>Collagenase 4</td>
<td>MMP-18</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Gelatinases</td>
<td>MMP-2</td>
<td>Gelatin, collagen IV, V, VI, X, elastin, fibronectin</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Collagens (IV, V, VII, X, and XIV), gelatin, entactin, aggrecan, elastin, fibronectin, osteonectin, plasminogen, MBP, IL-1β</td>
<td></td>
</tr>
<tr>
<td>Stromelysins</td>
<td>MMP-3</td>
<td>Collagens (III, IV, V, and IX), gelatin, aggrecan, perlecan, decorin, laminin, elastin, casein, osteonectin, ovostatin, entactin, plasminogen, MBP, IL-1β, MMP-2/TIMP-2, MMP-7, MMP-8, MMP-9, MMP-13</td>
</tr>
<tr>
<td>Stromelysin 1</td>
<td>MMP-10</td>
<td>Collagens (III–V), gelatin, casein, aggrecan, elastin, MMP-1, MMP-8</td>
</tr>
<tr>
<td>Stromelysin 2</td>
<td>MMP-11</td>
<td>Unknown (casein)</td>
</tr>
<tr>
<td>Matriylins</td>
<td>MMP-7</td>
<td>Collagens (IV, X), gelatin, aggrecan, decorin, fibronectin, laminin, elastin, casein, transferrin, plasminogen, MBP, β3-integrin, MMP-1, MMP-2, MMP-9, MMP-9/TIMP-1</td>
</tr>
<tr>
<td>Matriylin 1, Pump 1</td>
<td>MMP-26</td>
<td>Collagen IV, fibronectin, fibrinogen, gelatin, α (1)-proteinase inhibitor</td>
</tr>
<tr>
<td>Matriylin 2</td>
<td>MMP-14</td>
<td>Collagens (I–III), gelatin, casein, fibronectin, laminin, vitronectin, entactin, proteoglycans, MMP-2, MMP-13</td>
</tr>
<tr>
<td>Membrane-type MMPs</td>
<td>MMP-15</td>
<td>Fibronectin, entactin, laminin, aggrecan, perlecan; MMP-2</td>
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<td>MT1-MMP</td>
<td>MMP-16</td>
<td>Collagen III, gelatin, casein, fibronectin, MMP-2</td>
</tr>
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<td>MT2-MMP</td>
<td>MMP-17</td>
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<td>MT3-MMP</td>
<td>MMP-24</td>
<td>Fibronectin, but not collagen type I or laminin</td>
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<td>MT6-MMP</td>
<td>MMP-25</td>
<td>Progelatinase A</td>
</tr>
<tr>
<td>Others</td>
<td>MMP-12</td>
<td>Collagen IV, gelatin, elastin, casein, fibronectin, vitronectin, laminin, entactin, MBP, fibrinogen, fibrin, plasminogen</td>
</tr>
<tr>
<td>Macrophage metalloelastase</td>
<td>MMP-19</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>RASI</td>
<td>MMP-20</td>
<td>Amelogenin, aggrecan, COMP</td>
</tr>
<tr>
<td>Enamelysin</td>
<td>MMP-21</td>
<td>Unknown</td>
</tr>
<tr>
<td>Xenopus MMP</td>
<td>MMP-22</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chicken MMP</td>
<td>MMP-23</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cysteine array MMP</td>
<td>MMP-24</td>
<td>Unknown</td>
</tr>
<tr>
<td>No trivial name</td>
<td>MMP-25</td>
<td>Unknown</td>
</tr>
<tr>
<td>Epilysin</td>
<td>MMP-28</td>
<td>Unknown</td>
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</tbody>
</table>

MMP, matrix metalloproteinase; MBP, myelin basic protein; RASI, rheumatoid arthritis synovium inflammation; COMP, cartilage oligomeric matrix protein; TIMP, tissue inhibitor of metalloproteinases.
putatively relevant to vascular endothelial dysfunction and pathological remodeling.

Transcriptional Regulation of MMPs in Vascular ECs by Cyclic Strain

Signal transduction. The mechanisms by which the vascular endothelium recognizes and transduces mechanical stimuli are only now emerging. Vascular ECs detect hemodynamic forces via mechanosensor signaling systems [i.e., integrins, ion channels, G proteins, and receptor tyrosine kinases (RTKs)], which convert mechanical stimuli into chemical signals. Putative roles for platelet endothelial cell adhesion molecule (PECAM)-1 and glycosaminoglycans as vascular endothelial mechanosensors have also been the subject of recent investigations (40, 148). This leads to activation of second messenger systems including mitogen-activated protein kinase (MAPK) cascades, Akt, and PKC, subsequently leading to an increase in the activity of transcription factors such as activator protein (AP)-1 and -2, cAMP response element (CRE), early growth response protein (Egr)-1, and nuclear factor-κB (NF-κB). Binding of these factors to DNA leads to activation of numerous genes (including other transcription factors) that regulate EC fate decisions (71, 146) (Fig. 2). In this way, MMPs are tightly regulated by cyclic strain at the transcriptional level. Recent investigations in our laboratory (152), for example, have demonstrated that cyclic strain stimulates MMP-2 expression in bovine aortic endothelial cells (BAECs) by stimulating both p38- and extracellular signal-regulated kinase (ERK)-dependent pathways through activation of Gβγ and RTK signaling. A role upstream of ERK activation for the adaptor protein Shc was also confirmed in these studies (Fig. 2). In a related study, Wang and coworkers (155) demonstrated induction of MMP-2/14 expression in human umbilical vein endothelial cells (HUVECs) by cyclic strain, an event mediated, at least in part, by TNF-α, likely via a JNK pathway. Evidence suggesting the involvement of the AP-1 transcription factor in these events was also presented by these authors (Fig. 2). This latter finding is of particular interest. An earlier study by Du et al. (32) demonstrated that exposure of BAECs to a cyclic strain regimen identical to that used in our own study (152) did not show any significant induction of AP-1, CRE, or NF-κB, whereas induction of all three factors was observed under...
similar conditions in human aortic endothelial cells (HAECs) and HUVECs. These findings are in marked contrast to the previously described activation of AP-1 and NF-κB in BAECs by shear stress (47, 63). More importantly, however, they suggest that these factors are not involved in cyclic strain-induced MMP-2 expression in BAECs observed in our studies. Although as yet undetermined, other strain-inducible transcription factors (e.g., AP-2, CRE-like transcription factors, Egr-1) may be involved, however (139, 164). These observations may partially explain the divergent effects of cyclic strain on vascular endothelial gene expression (and phenotype) from different vascular beds and species and also underscore the differences in EC responses to cyclic strain and shear stress.

With the exception of the recent studies by von Offenberg Sweeney et al. (152) and Wang et al. (155), relatively few attempts have been made to definitively identify the upstream signaling components and indeed the transcription factors engaged by cyclic strain to directly modulate endothelial MMP expression (and particularly soluble MMP expression). Recent studies by Yamaguchi et al. (164) and Yun et al. (168) demonstrate upregulation of Egr-1 expression and activity in rat microvascular ECs in response to cyclic strain and shear stress, respectively. Indeed, with respect to cyclic strain, this process may proceed via a Ras/Raf-1/ERK pathway (161). The aforementioned authors also show that upregulation of Egr-1 is necessary for the force-mediated increase in endothelial MT1-MMP expression (a process that most likely involves increased Egr-1 binding to the MT1-MMP promoter, coupled with the serine phosphorylation and competitive displacement of Sp1) (164, 168). Uprogulation of Egr-1 has also been shown to correlate with increased MT1-MMP expression (as well as increased expression of MMP-2 and -9) in a rabbit model of carotid artery arteriovenous fistula (AVF), an in vivo model that mimics arterial remodeling due to elevated flow/strain (132). Also worthy of note, Egr-1-mediated upregulation of MT1-MMP has been reported in vascular ECs stimulated to undergo angiogenesis, albeit following matrix stimulation (as opposed to cyclic strain stimulation) (50). Thus, Egr-1 appears to be essential for both force-dependent and -independent induction of MT1-MMP within the vascular endothelium.

Reactive oxygen species. The oxidative state of the vascular endothelium is fundamental to vascular health and remodeling. In vascular pathologies such as atherosclerosis and diabetes mellitus, levels of ROS such as hydrogen peroxide, superoxide anions, hydroxyl radicals, and peroxynitrite are all elevated (121, 149). Indeed, cyclic strain is believed to be a significant contributor to this increase in oxidative stress (156). Much recent evidence now indicates that ROS can act as second messengers during cyclic strain-mediated signal transduction, leading to induction of gene expression. Frye and coworkers (39), for example, recently determined by cDNA microarray analysis that many of the genes regulated by cyclic strain in vascular ECs have antioxidant properties, suggesting that oxidative mechanisms direct EC adaptation to strain. Cyclic strain was also previously shown to induce rapid and sustained elevation in endothelial ROS levels via upregulation of NAD(P)H oxidase (70, 91) and via ROS release from mitochondria (3). In both studies, the increase in oxidative stress was accompanied by increased mobilization of the transcription factor NF-κB, an effect that could be attenuated by pretreatment of ECs with either NAD(P)H oxidase inhibitors or antioxidants (Fig. 3). Moreover, Wang et al. (156) suggest that these events likely proceed along a strain-sensitive integrin/PKC signaling axis, leading to the observed elevation in intracellular ROS levels and subsequent induction of NF-κB (Fig. 3). Cyclic strain-induced elevation in endothelial ROS levels has also been shown to increase AP-1 and Egr-1 expression and DNA binding activity (161–162). Although no studies exist, to our knowledge, that directly address the cyclic strain-mediated transcriptional regulation of MMPs via ROS production in vascular ECs, existing data strongly support this hypothesis. In vascular pathologies such as diabetes mellitus and atherosclerosis where cyclic strain is a contributory factor, areas of high oxidant stress (e.g., plaques) exhibit elevated MMP-2 and MMP-9 mRNA and protein levels, consistent with elevated remodeling. More importantly, these increases can be attenuated by antioxidant and catalase treatment (121, 149). The work of Galis et al. (41), for example, clearly demonstrates that elevation of MMP-2 and -9 activity (and MMP-9 expression) in aortic lesions isolated from hypercholesterolemic rabbits can be attenuated by treatment with N-acetyl-l-cysteine, a ROS scavenger. In addition, VCAM-1-dependent activation of NAD(P)H oxidase, a necessary step for VCAM-1-dependent lymphocyte migration, has been shown to involve ROS-dependent upregulation of MMP expression and activity in vascular ECs (29). Furthermore, in support of an earlier article by Faller (34), Kolev et al. (75) recently demonstrated induction of MMP-9 expression via an NF-κB pathway in human brain microvascular ECs in response to hypoxia (a feature of vascular remodeling pathologies). The strain-dependent elevation of ROS in vascular ECs leading to Egr-1 induction (161) is also significant when one considers that strain-dependent upregulation of endothelial MT1-MMP proceeds via an Egr-1 pathway (164), thus implicating direct involvement of ROS in the latter process. In light of these collective observations, therefore, it appears highly likely that ROS are engaged directly by cyclic strain to modulate MMP expression within the vascular endothelium, with direct consequences for vessel wall remodeling.

Nitric oxide synthase—nitric oxide. NO is a short-acting, potent vasodilator crucial to maintenance of vascular integrity. NO is generated by NOS, of which both constitutively expressed (endothelial NOS or eNOS) and inducible (iNOS) forms exist in vascular cell types. Vascular ECs constantly release NO, which has multiple effects on vascular cells including regulation of platelet aggregation and leukocyte adhesion as well as regulating migration and proliferation of vascular ECs/SMCs (125). Moreover, the rate of NO production by ECs in vivo and in vitro can be influenced by numerous factors, most notable of which are blood flow-associated hemodynamic forces. Indeed, several studies have reported upregulation of endothelial NO (in parallel with elevated eNOS expression) following cyclic strain or shear stress of vascular ECs, consistent with the atheroprotective vasodilatory environment promoted by these forces within the vessel (5, 106, 170). The detailed molecular mechanism of how NO affects cellular physiology remains unclear, while studies of NO effects on cells have yielded controversial results. Reports have demonstrated both promigratory (72, 88) and antimigratory (14, 77, 79, 143) effects of NO on vascular ECs. As migration inevitably involves matrix remodeling, the relationship between NO and MMPs has received some attention. NO-mediated inhibi-
tion of MMP-2 and -9 expression/activation in vascular ECs was recently shown to accompany blockade of migration (13, 14). These findings are consistent with related studies that show that NOS inhibition leads to increased MMP-2 activity in coronary vessels (90), whereas NOS overexpression (in SMCs) leads to reduction of MMP-2 activity and, consequently, migration (49). By contrast, another recent study has suggested that NO-mediated induction of MMP-13 stimulates BAEC migration (88).

Although not directly addressed within the existing literature, it appears likely that cyclic strain-mediated transcriptional (and posttranscriptional/translational) regulation of MMPs in vascular ECs may occur, at least in part, indirectly through eNOS induction and thus NO production. Although the signaling pathway(s) mediating these events has yet to be identified, the recent work of Chen and Wang provides some clues. These authors recently determined that NO-mediated downregulation of MMP-13 stimulates BAEC migration (88).

Fig. 3. Putative involvement of reactive oxygen species (ROS) in cyclic strain-mediated transcriptional regulation of MMP-2 and -9 in vascular ECs. Cyclic strain leads to elevated intracellular ROS levels via NAD(P)H oxidase activation and/or release of ROS from mitochondria. Integrin activation of a PKC-sensitive pathway following cyclic strain can also lead to elevated ROS levels and consequently to mobilization of the transcription factor NF-κB, ultimately leading to modulation of MMP/TIMP gene expression. It should also be noted that strain-dependent elevation of ROS can lead to mobilization of other transcription factors such as AP-1 and Egr-1. Blue, protease; gray, kinase; yellow, ROS; pink, nucleotide exchange factor; green, transcription factor. RGD, Arg-Gly-Asp.

Cyclooxygenase 1/2—prostaglandins. Constitutive and inducible cyclooxygenases (COX-1 and -2, respectively) and their associated prostaglandin products have been firmly implicated in vascular endothelial remodeling and are subject to mechanoregulation (74, 106, 129). Research has shown that increased expression of COX-2, leading to elevation of prostaglandins PGE2 and PGI2, is involved in inflammatory responses (e.g., atherosclerotic plaque formation) (55) and increased angiogenesis (e.g., tumor and plaque microvasculature formation) (42, 101, 141). As these events require activation of MMPs, the regulatory interaction between prostaclin production and MMP expression has received some attention (for review see Ref. 42). Of particular relevance, recent studies by Sun et al. (141) and Hong et al. (55) demonstrate that COX-2 contributes to tumor angiogenesis and plaque formation, respectively, via upregulation of MMP-9 and MT1-MMP expression. Similarly, exposure of retinal microvascular ECs to hypoxia leads to cytosolic phospholipase A2-dependent production
of prostaglandins, which in turn causes increased mRNA expression of MMP-2, MT1-MMP, and TIMP-2, leading to upregulation of tube formation (107). These collective data clearly point to a dynamic relationship between prostaglandin function and MMP expression. As hemodynamic forces contribute profoundly to the initiation and progression of both angiogenesis and atherosclerosis, and considering the mechanosensitivity of prostaglandin production, these collective observations suggest that cyclic strain-mediated regulation of MMP expression within the vascular endothelium likely proceeds, at least in part, via prostaglandin signaling. Further research will conclusively establish this.

Posttranscriptional regulation of MMPs. Alteration of mRNA stability represents an important mechanism for posttranscriptional regulation of gene expression. Regulation of mRNA stability in vascular ECs by shear stress and hypoxia, for example, has been reported (61, 83, 136, 158). Unfortunately, very few studies have focused on posttranscriptional regulation of mRNA stability by cyclic strain, although some recent studies suggest this may be applicable to regulation of MMP expression. Jozkowicz and coworkers (68) recently demonstrated, for example, that prostaglandin PGJ₂, a force-inducible prostacyclin (142), can upregulate MMP-1 expression in human microvascular ECs, not by changing promoter activity but by increasing stability of MMP-1 mRNA. Similarly, NO-mediated reduction of MMP-9 mRNA stability via inhibition of HuR expression has also been reported, albeit in rat renal mesangial cells (also known to be chronically subjected to biomechanical stimulation in vivo) (1, 33). Although clearly evocative, cyclic strain-mediated regulation of endothelial MMP expression by alteration of mRNA stability has yet to be definitively proven, however.

Posttranslational Regulation of MMPs in Vascular ECs by Cyclic Strain

MMP activation. Generation of “active” MMPs from proenzyme forms typically requires proteolytic cleavage within the pro-MMP domain either by serine proteases or other activated MMPs and, in some instances, TIMPs (99). Activation of pro-MMP-2, for example, has been extensively studied in vascular ECs (and other systems) and so will serve as an ideal case study here. Pro-MMP-2 activation involves its complex interaction with MT1-MMP (MMP-14) and TIMP-2 (31, 171). During this event, the NH₂-terminal of TIMP-2 binds to an activated MT1-MMP on the cell surface, leaving its COOH-terminal domain free. The hemopexin domain of pro-MMP-2 binds to the COOH-terminal domain of TIMP-2 and is subsequently cleaved by an adjacent unbound MT1-MMP activity. After the initial cleavage of pro-MMP-2, a residual portion of the propeptide is removed by another MMP-2 molecule to yield a fully mature form of MMP-2 (for review see Ref. 98).

Cyclic strain-mediated increase in activity of endothelial MMP-2 and -9 has been reported by our laboratory (152) and others (130). Likewise, strain-induced increases in MMP-2 activity, in conjunction with MT1-MMP activity, have been reported by Wang et al. (155) and Haseneen et al. (54) in HUVECs and pulmonary microvascular ECs, respectively. Coinduction of MMP-2 and MT1-MMP following strain/stretch have also been reported for other systems (10, 123). Cyclic strain-mediated upregulation of TIMP-2 mRNA and protein has also been reported in microvascular ECs (100). Evidence clearly indicates, therefore, that the process of MMP activation within the vascular endothelium is a target for cyclic strain.

Regulation of MMP activity. TIMPs represent a pivotal mechanism for regulation of MMP activity within the extracellular domain of the vascular endothelium. Mammalian TIMPs are dual-domain molecules comprising an NH₂-terminal domain of ~44 amino acids and a larger COOH-terminal domain of ~65 amino acids (159). There are currently four TIMPs identified in mammalian systems (TIMP-1 to -4), which range in size from 20 to 29 kDa and are expressed in a variety of cell types including fibroblasts, keratinocytes, osteoblasts, and vascular ECs/SMCs (115). TIMPs have the ability to reversibly inhibit MMPs in a 1:1 stoichiometry. Moreover, although they share a high degree of homology, significant differences in their inhibitory profiles have been reported (11). While their roles in regulating MMP activity in various systems have been well established, TIMP sensitivity to cyclic strain mechanoregulation in vascular ECs has received relatively scant attention. For activation of pro-MMP-2 to occur, researchers have shown that coordinate interaction of TIMP-2 with MT1-MMP is essential. Interestingly, whereas the COOH-terminal domain of TIMP-2 participates in the docking and activation of MMP-2, the NH₂-terminal region is an MMP inhibitor. Thus low levels of TIMP-2 may promote MMP-2 activation while higher levels of TIMP-2 lead to inhibition by saturation of MT1-MMP binding sites required for removal of the propeptide domain of pro-MMP-2 (35). Considering the sensitivity of endothelial MT1-MMP to cyclic strain (54, 132, 155, 164), one can reasonably assume that expression of TIMP-2, and indeed other TIMPs, is also sensitive to cyclic strain within this context. In this regard, a recent paper by Namba et al. (100) demonstrates upregulation of TIMP-2 (and TIMP-1) protein in retinal microvascular ECs following strain. By contrast, MMP-2 and TIMP-2 levels were unchanged by cyclic strain in human vascular SMCs (165). Both positive and negative modulation of TIMP-2 (and TIMP-1) mRNA/protein levels by mechanical stretch have also been reported for other cell systems (46, 163, 166), and the sensitivity of endothelial TIMP-2 mRNA/protein levels to shear stress has also been documented (128, 132). Based on these findings, TIMP expression and function within the vascular endothelium are almost certainly mechanosensitive and, as regulation of MMP-TIMP balance is critical to vascular remodeling, mechanoregulation of TIMP expression by cyclic strain (and shear stress) is likely to be an important route for control of extracellular endothelial MMP activity.

The fibrinolytic system also impacts significantly on regulation of active MMP levels within the endothelium. This system, comprising plasminogen activators [i.e., uPA and tissue-type plasminogen activator (tPA)] and their inhibitors (i.e., PAI-1 and -2), regulates conversion of plasminogen to plasmin, which has been linked to activation of MMP-1, -2, -9, -10, and -13 (12, 13, 28, 85). Moreover, with respect to MMP-9 activation in particular, this has direct consequences for EC fate and angiogenesis (12, 28, 154). Regulation of the endothelial fibrinolytic system by cyclic strain has also received considerable attention. Sumpio and coworkers (59, 139), for example, demonstrated upregulation of tPA in BAECs and human saphenous vein ECs in response to chronic cyclic strain, while...
seeing no effect on extracellular PAI-1 levels in the latter cell type. By contrast, Ulfhammer et al. (150) report a transient upregulation of tPA and uPA mRNA expression in HAECs (after 6 h at 10% cyclic strain) followed by a sustained downregulation in both activators from 48 h onward; this was accompanied by a sustained increase in PAI-1 expression. Cheng et al. (15) and von Offenberg Sweeney et al. (154) also report cyclic strain-dependent increases in PAI-1 and uPA expression, respectively. The latter study by von Offenberg Sweeney and coworkers is particularly interesting. In parallel with strain-dependent induction of uPA, MMP-2, and MMP-9 expression in BAECs, these authors demonstrated that small interfering RNA (siRNA)-directed blockade of either uPA or MMP-9 (but not MMP-2) expression attenuated strain-induced endothelial tube formation by ~85% and 41%, respectively (154). This suggests that adaptation of endothelial angiogenic phenotype to cyclic strain in this instance proceeds, at least in part, along a uPA/MMP-9 signaling axis, although other uPA/MMP axes cannot be ruled out. These findings are consistent with the earlier findings of Brodsky et al. (12) and Davis et al. (28) and, on a broader level, strongly implicate the fibrinolytic system in directly mediating cyclic strain-dependent EC fate decisions via regulation of MMP activity.

Cyclic Strain-Mediated Regulation of Vascular Endothelial Cell Fate: Putative Role of MMPs

Angiogenesis—EC migration and tube formation. MMPs are vital to the process of angiogenesis. They confer on ECs and their supporting cellular elements the ability to remodel their immediate ECM environment, a critical process for enabling cell proliferation and migration, as well as enabling the formation, stabilization, and regression of tubular networks (27, 65, 66, 105). The enzymes that control basement membrane degradation and the initiation of angiogenesis, for example, include MMP-2, MMP-3, MMP-9, MMP-10, and MT1-MMP (which, in conjunction with TIMP-2, activates MMP-2). Although all are induced during tubular morphogenesis, their precise contributions to the angiogenic process have yet to be fully delineated, and indeed the influence of any particular MMP may depend on the vascular bed or the EC type involved. Most likely they operate in precise combinations to control EC invasion through the basement membrane during the sprouting phase of angiogenesis. In addition to basement membrane degradation, these MMPs may also inactivate a constitutive inhibitor of EC sprouting morphogenesis, which may be present within basement membranes to prevent sprouting in a quiescent vessel and possibly be produced by other supporting cells such as pericytes (for review, see Ref. 27). With respect to the aforementioned MMPs, investigations conducted in our laboratory (152) and by others (93, 155, 164) confirm that cyclic strain upregulates their expression, activity, and with respect to soluble MMPs (e.g., gelatinases MMP-2 and MMP-9), their secretion. Moreover, we recently demonstrated (154) that exposure of BAECs to chronic equibiaxial cyclic strain (5% strain, 1 Hz for 24 h) results in almost twofold increases in both EC migration and tube formation, indexes of a proangiogenic endothelial phenotype. These increases were Gα protein dependent and protein tyrosine kinase independent (although roles for RGD-dependent integrins and uPA in these events were also established). More importantly, siRNA-directed attenuation of endothelial MMP-9, but not MMP-2, significantly decreased both strain-induced cell fates, appearing to rule out a significant role for MMP-2 in strain-induced angiogenesis (154). Consistent with this conclusion, we demonstrated (152) that genistein, a RTK inhibitor that blocks strain-induced endothelial MMP-2 upregulation, also had no effect on this process. By contrast, MMP-9 appears to have a significant, albeit poorly understood, role in cyclic strain-induced angiogenesis, a conclusion consistent with previous studies that also suggest roles for MMP-9 in ligand-induced endothelial migration and tube formation (57, 89, 120). To our knowledge, this is the first instance in which a role for MMP-9 in the context of force-induced angiogenesis has been reported, and it represents an important functional divergence between MMP-2 and -9 with respect to vascular remodeling, most likely reflecting differences in the coordinate interaction between either MMP and other mechanosensitive substrates involved in angiogenesis.

Although there are no previous studies, to our knowledge, that directly address the putative involvement of MMP-2 in cyclic strain-induced angiogenesis, these results are particularly interesting in light of earlier publications that indicate a stimulatory role for MMP-2 in both hypoxia- and ligand-induced endothelial migration and tube formation in vitro (9, 104, 157, 160) and angiogenesis in vivo (48, 110). A recent study by Rivilis and coworkers (123) identifying a possible role for MMP-2 in capillary formation in response to skeletal muscle stretch (a comparative stimulus to cyclic strain) is also worthy of mention. Also of relevance, the investigations of von Offenberg Sweeney et al. have been extended to show that although strain-induced endothelial MMP-2 had no apparent effect on vascular EC angiogenic phenotype (i.e., migration and tube formation), it was found to significantly reduce SMC migration (153). In this study, the authors suggest that the upregulation of endothelial MMP-2 in response to cyclic strain putatively leads to interaction between MMP-2 and an EC target protein, with consequences for generation of an as yet unidentified SMC-specific antimigratory component [although an earlier study by Proia et al. (119) implicates endothelium-derived PAI-1 in this scenario]. These findings reveal a potentially novel role for strain-induced endothelial MMP-2 in regulating vascular SMC fate. Interestingly, the same study also demonstrated that strain-induced endothelial MMP-9 had no impact on SMC migration, again highlighting the functional divide between MMP-2 and -9 with respect to force-mediated vascular remodeling.

Apoptosis. Research has previously shown that apoptosis can be suppressed by physiological cyclic strain (and shear stress) in ECs via phosphatidylinositol 3-kinase (PI3-kinase)-mediated activation of Akt, leading to phosphorylation of Bad (51, 87). Whereas studies have not directly addressed the participation of MMPs in force-mediated apoptosis in vascular ECs, evidence clearly points to their involvement. Langlois et al. (78) recently demonstrated, for example, that the ability of MT1-MMP to induce endothelial morphogenic differentiation during angiogenesis, a strain-regulated event (see Angiogenesis—EC migration and tube formation), involves its activation of a caspase-3-dependent pathway. Moreover, the disruption of shear stress and cyclic strain levels resulting from the reduction in cardiac output characteristic of congestive heart failure correlates with cardiac and aortic remodeling, endothelium-
myocyte uncoupling, and EC apoptosis putatively stemming from MMP-9 activation (108). Recent work by Ben-Yosef et al. (9) also shows that hypoxia-induced endothelial apoptosis, a putative feature of atherosclerotic plaque formation originating from disruption of normal endothelial mechanotransduction pathways, occurs in an MMP-2-dependent manner. These studies demonstrate that hemodynamic force-mediated apoptotic events within the vascular endothelium putatively involve activation and recruitment of MMPs, with significant physiological and pathological implications.

Barrier function. Endothelial barrier function (i.e., permeability) is maintained by the regulated apposition of tight junction and adherens protein complexes between adjacent ECs. Regulation of barrier integrity is crucial for vascular homeostasis and is a central pathophysiological mechanism of many vascular processes including wound healing and vascular disease progression (6, 53, 151). EC-EC junctional stability may also enhance basement membrane matrix stability by facilitating the continued deposition of basement membrane components in a polarized basal direction and is most likely responsible for EC tube stabilization and a quiescent phenotype (94, 167). Vascular pathologies exhibiting altered vessel hemodynamic loading with associated remodeling (e.g., atherosclerosis, restenosis, retinopathy, inflammatory lung disease, sepsis, edema) frequently correlate with compromised endothelial barrier integrity (53, 145, 151), allowing one to hypothesize a dynamic regulatory association between endothelial permeability and hemodynamic stimuli. In this regard, we recently demonstrated (21) that physiological cyclic strain significantly upregulates vascular endothelial barrier function by altering the phosphorylation state and localization of the tight junction proteins occludin and ZO-1. Although this is not addressed in this or indeed any other study, other published findings suggest a role(s) for MMPs in these mechanically regulated events. Membrane-associated proteinases are known to facilitate proteolytic disassembly of junctional contacts and include ADAM (a disintegrin and metalloprotease)-10, ADAM-15 (concentrated in junctions of both endothelial and epithelial cells) (52, 56), and MT-MMPs (23). Roles for soluble proteinases such as MMP-3 (stromelysin-1) in vascular EC barrier regulation have also been reported (124), as have roles for MMP-2 and -9. With respect to the latter, studies show that elevated MMP-9 is responsible for reduction of barrier function in bovine retinal ECs (BRECs) via proteolytic cleavage of occludin (8). Mori et al. (97) also demonstrated that elevated MMP-9 is responsible for loss of barrier function in edema following traumatic brain injury, most likely via proteolytic cleavage of ZO-1. Proteolytic inactivation of tight junction proteins due to elevated MMP-2 and -9 levels has also been shown to be responsible for decreased barrier function at the blood-retinal barrier in vivo during early diabetic retinopathy (45). Also worthy of note, Miyamori and coworkers (96) showed previously that activation of pro-MMP-2 by MT1-MMP can be mediated by claudin family members, major components of tight junctions. Although not directly addressed in these studies, a regulatory hemodynamic component is apparent. Both diabetic retinopathy and edema are characterized by pathological levels of cyclic strain (and shear stress), which may contribute to, or be causative of, the MMP induction seen in these studies (45, 97).

At first glance, these studies appear to conflict with our own in vitro findings, which demonstrate that cyclic strain elevates EC barrier function (21) in parallel with MMP-2 and -9 levels (152). This may reflect a hemodynamic balance between MMP induction and barrier upregulation, with the latter favored at physiological levels of mechanical load. However, the studies of Collins et al. (21) never extended beyond the physiological range of loading (5% equibiaxial cyclic strain, 24 h, 60 cycles/min) and were also conducted in peripheral macrovascular ECs (i.e., BAECs). Although yet to be demonstrated, exposure of BAECs to pathologically high levels of cyclic strain would most likely result in breakdown of barrier integrity coupled to a dose-dependent elevation in MMP-2 and -9 activities. The possibility that force-mediated regulation of endothelial barrier function may proceed in an MMP-independent manner, particularly at physiological or subphysiological levels of strain, is also worth considering. In view of the relative dearth of information in this area, therefore, more studies are clearly required to enhance our understanding of how mechanical forces work in concert with MMPs to modulate endothelial barrier properties because novel strategies to preserve barrier integrity could have profound clinical impact.

Cyclic Strain and Endothelial Dysfunction: Relevance to Vascular Pathology

The vascular endothelium senses and controls biomechanical stimuli by adapting arterial dimensions to blood flow, a process referred to as vascular remodeling. Force-mediated remodeling occurs on a continual physiological basis, therefore, to maintain vessel architecture and integrity. As remodeling requires degradation and reorganization of the ECM, the relationship between biomechanical stimulus and MMP-TIMP balance within the endothelium (and indeed within the medial and adventitial layers of the vessel wall) is critical. In this regard, endothelial dysfunction or injury leading to hemodynamic dysregulation of this balance is a principal initiator and contributor to vascular occlusive pathologies such as atherosclerosis (73, 118), restenosis/IM (e.g., vein graft occlusion, graft coronary vasculopathy) (76, 103, 112), and HT (34, 122). The following sections examine this phenomenon in more detail with emphasis on common remodeling pathologies.

Atherosclerosis. Hemodynamic forces interacting with an active vascular endothelium are responsible for localizing atherosclerotic lesions in a nonrandom pattern of distribution. Essentially, plaque formation tends to occur at sites of arterial curvature and branching, where cyclic strain and hydrostatic pressure are reduced/perturbed and blood flow shear stress is low and oscillatory (37, 44). Thus improper biomechanical stimulation of the vascular endothelium precipitates endothelial dysfunction, the starting point of lesion formation. Moreover, the severity of dysfunction can be exacerbated by other factors including HT, homocysteine, oxidized low-density lipoprotein (ox-LDL), toxins (e.g., nicotine), and infectious agents (e.g., Chlamydia, Helicobacter pylori, viruses) (73).

Early lesion formation is a slow-grade inflammatory process characterized by upregulation of endothelial LDL receptor expression and increased adherence of monocytes, macrophages and T cells to the EC surface. This is followed by accumulation of ox-LDL, activated ligands/cytokines, and ul-
ultimately macrophages/SMCs within the subendothelial layer, culminating in intraluminal plaque formation (73, 118).

Reduction in EC barrier integrity, a feature of early lesion formation, in response to subphysiological levels of cyclic strain has recently been demonstrated with BAECs in vitro in our laboratory (21) and points to a putative in vivo mechanism whereby reduced or attenuated cyclic strain (and shear stress) within the local microenvironment of the lesion may facilitate eccentric plaque maturation. Reduced expression and activation of MMP-2 and -9 in vascular ECs at subphysiological levels of cyclic strain (152) also likely contribute to early lesion formation in vivo. The recent findings of von Offenberg Sweeney et al. (153), for example, suggest that the reduction in endothelium-derived MMP-2 in response to low cyclic strain may lead to reduced production of endothelial PAI-1, an antimigratory molecule, thereby permitting increased migration of medial SMCs into the intraluminal plaque core (119).

As already mentioned, progression of atherosclerosis can give rise to the development of a mature plaque that is vulnerable to rupture, leading to intraluminal thrombosis and acute coronary syndrome (73). Maturation of plaques has been reported to correlate with significant alteration of local hemodynamic profile within the plaque vicinity (i.e., increased stationary/cyclic strain and shear stress) (4, 26, 134). This likely contributes to plaque instability by inducing lesional upregulation of MMP-2 and -9 levels in SMCs and immune cells (note that mature vulnerable plaques lack a functional endothelium), thereby promoting weakening and subsequent rupture of the fibrous cap (30, 109, 121, 135).

**Intimal hyperplasia.** IH is the process by which the cell population increases within the innermost layer of the arterial wall. It occurs pathologically in atherosclerosis, HT, and organ transplantation and after balloon angioplasty, stenting, and aortocoronary saphenous vein grafting. Underlying causes of IH are migration and proliferation of vascular SMCs provoked by endothelial dysfunction/injury, oxidative stress, and, most importantly, cyclic strain (102, 116). The latter procedure, for example, autogenous vein grafting, is a common and effective method to treat occlusive vascular disease. The necessary use of pressure distension during surgical preparation of saphenous veins, however, invariably leads to compromise of endothelium integrity, subsequently promoting undesirable vascular remodeling and decreased graft patency (>50% reclosure rate within 10 yr) (19, 24, 144). Prevention of intraoperative injury to the endothelium is therefore of primary importance and is the rationale fueling development of new minimal handling “no touch” techniques for saphenous vein harvest (24, 25). Successful adaptation of saphenous vein to the level of pulsatile circumferential deformation (i.e., cyclic strain) common to arterial circulation is absolutely critical to proper functioning of the graft and requires an intact functional endothelium. Increased endothelial MMP-2 expression in response to elevated cyclic strain, with antimigratory consequences for the underlying medial SMCs, may contribute to the protective effect of the endothelium within this context (153), although this is still somewhat speculative and requires further investigation. In the absence of an intact functional endothelium, strain-mediated upregulation of SMC-derived MMP-2 leads to increased proliferation and migration of SMCs and, consequently, IH and vein stenosis (19, 95, 131, 147). This is particularly relevant in the anatomic regions of the recipient artery, where cyclic strain is as much as twofold higher than in normal artery (113). Stent implantation may be employed to prevent pulsatile distension of the vessel wall and thus attenuate cyclic strain-induced changes in SMC gene expression and the later development of IH (116). However, sustained (i.e., nonpulsatile) outward distension of the vessel wall caused by stenting can lead to in-stent restenosis, most likely via SMC MMP-9 induction (36, 43).

**Hypertension.** The pathogenesis and pathophysiology of HT involve a number of vascular components, including alteration of vessel structure (remodeling), mechanics (stiffness), and ultimately function. Vascular remodeling in particular is a predominant feature of HT (e.g., pulmonary HT), and is characterized by a reduced lumen diameter and thickening of the vessel wall, resulting in increased media-to-lumen ratio. Remodeling in HT primarily stems from increased expression and turnover of ECM proteins (e.g., collagen, elastin, laminin) coupled with medial SMC hyperplasia (69). Changes in the mechanical properties of the vessel, particularly vessel stiffness, may also contribute to reduced lumen diameter. Ultimately these alterations lead to increased vascular resistance and reduced compliance (62, 64).

HT is characterized by elevated blood pressure and cyclic strain, which undoubtedly contribute to the inward remodeling and compromised vessel function associated with this disease, likely via MMP induction within the vascular endothelium (as well as within the medial and adventitial layers of the vessel wall). In two different rat models of progressive pulmonary HT, for example, Frisdal et al. (38) demonstrate induction of MMP-2 in all layers of the vessel. Consistent with this, Spiers et al. (137) also recently demonstrated that aging and the development/progression of HT are associated with increases in total aortic MMP-2 activity levels. Interestingly, ET receptor blockade with bosentan (i.e., dual ETA/ETB blockade) was found to attenuate this induction, implicating cross talk between the ET and MMP-TIMP systems (137). Although not directly indicated in these studies, one can speculate that some of the MMP-2 induction occurs within the vascular endothelium; however, this requires more definitive investigation. Furthermore, other studies have demonstrated that cyclic strain-induced endothelial MMP-9 contributes to hypertensive remodeling in rats and humans (126).

**Summary**

A wealth of research in recent years has highlighted the importance of the vascular endothelium in regulating blood vessel homeostasis. By virtue of its unique location between the vessel wall and the bloodstream, the endothelium is well placed to detect both humoral and biomechanical stimuli and to transduce these signals effectively to the underlying effector SMCs. Changes in blood flow pattern arising from physiological, developmental, and pathological phenomena can disrupt the normal hemodynamic cues detected by vascular ECs and lead to adverse remodeling of the vessel wall. As remodeling needs an orderly degradation/modification of the ECM, force-dependent modulation of MMP levels is therefore inevitable.

Consistent with this theme, this review has summarized our current knowledge of how cyclic strain, through activation of specific signaling pathways leading to modulation of MMP levels, influences vascular endothelium biology. Unlike shear
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stresses, the effect of cyclic strain (i.e., the tensile component of blood pressure) on endothelial activation has received comparatively little attention. Much recent work from both our own laboratory and others, however, has helped to address this knowledge deficit and provides clearer evidence toward a physiologically significant role for cyclic strain in differentially regulating endothelial MMP levels (and specifically MMP-2, MMP-9, and MT1-MMP), with direct consequences for endothelial phenotype (migration, apoptosis, etc.) and function (permeability, angiogenesis, etc.). This contributes to a better overall understanding of the biological consequence and mechanoregulation of MMP activity within the endothelium, which is critical to the design and application of effective MMP blockade strategies in occlusive vascular diseases.

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Invited Review


