Matrix Metalloproteinase-8 and the Regulation of Blood Pressure, Vascular Inflammation, and Atherosclerotic Lesion Growth

Ziad Mallat

T he description in the early 1990s of intriguing associations between the expression/activity of specific matrix metalloproteinases (MMPs) and signs of plaque inflammation and matrix degradation1–3 spurred an impressive effort of research to precisely define the roles of MMPs in both the development and complications of atherosclerosis. After two decades of research in this area, mechanistic studies using genetically manipulated mice with deletion or overexpression of specific MMPs, complemented with genetic epidemiological studies, have revealed more complex and, sometimes divergent, roles of MMPs in the modulation of lesion development, progression and complications.4 There are many potential explanations for these findings. Ambivalent effects of specific MMPs have been reported in different models of atherosclerosis,5 emphasizing the urgent need for carefully relevant animal models of disease complications. For example, even the use of the brachiocephalic artery of apolipoprotein E knockouts (ApoE−/−) as a model of type-specific plaque rupture did not allow to differentiate between the roles of MMPs in plaque development versus plaque complications. A close look at this model reveals that the number of buried fibrous caps is highly proportional to lesion size, independently of mouse genetic background and MMP expression.6 The complex role of MMPs in atherosclerosis could be attributed to the diversity of biological processes relevant to this disease, which are subject to tight control by MMPs and the modulation of which could have divergent consequences for lesion development and fibrous cap stability. The MMP-controlled processes include those classically related to matrix remodeling, vascular smooth muscle cell migration and proliferation, endothelial cell loss and repair, angiogenesis,7 and macrophage invasiveness. However, matrix-unrelated effects of MMPs8 should not be overlooked. Among these, the control of inflammation through chemokine cleavage9 or the control of blood pressure through the modulation of angiotensin (Ang) I cleavage by MMP-8,11 as shown by Laxton et al10 in this issue of Circulation Research, may greatly impact atherogenesis and plaque stability.

MMP-8, also known as collagenase-2 or neutrophil collagenase, has previously been involved in the process of atherosclerosis, although indirectly through association studies showing increased expression of this MMP in vascular cells and macrophages12 of rapidly progressing lesions13 and elevated serum levels of MMP-8 in individuals at risk for adverse cardiovascular outcome.14 Laxton et al10 now provide more mechanistic experimental data combined with genetic approaches in humans to support a pathogenic role for MMP-8 in the development and progression of atherosclerosis. Their results indicate that inactivation of MMP-8 in ApoE−/− mice reduces atherosclerotic lesion size and limits vascular inflammation as exemplified by reduced endothelial vascular cell adhesion molecule-1 expression and plaque macrophage accumulation. MMP-8 deficiency also improved lesion healing, as revealed by a higher collagen content and a trend toward enhanced smooth muscle cell accumulation. However, atherosclerotic lesion extent was determined using en face oil red O staining of thoracic aortas, whereas plaque composition was assessed at a distinct vascular site using transversal sections of the aortic root, which complicates data interpretation particularly regarding the relationship between plaque composition and lesion size.

The first temptation is to try to attribute these changes in lesion size and composition to the matrix-degrading properties (particularly on type I collagen) of MMP-8. Indeed, matrix degradation impairs collagen accumulation and should facilitate vascular wall infiltration by monocytes/macrophages, potentially leading to initial acceleration of atherosclerosis. However, reduced matrix accumulation might ultimately limit atherosclerotic plaque growth. In this regard, lesion assessment in MMP-8−/− deficient animals was unfortunately restricted to a single time point, which did not allow to draw conclusions about the potential roles of MMP-8 in lesion maturation and progression. Interestingly, Laxton et al have also examined other matrix-unrelated properties of MMP-8 that could potentially account for its proatherogenic activities. Their data suggest that MMP-8 proatherogenic role is most likely related to the modulation of Ang II production and to the impact of Ang II modulation on blood pressure and vascular inflammation (Figure). Based on previous studies indicating that MMP-8 cleaves Ang I to generate fragments of Ang II and Ang(1–7),15 Laxton et al have identified an in vivo role for MMP-8 in the production of vasoactive Ang II and the control of blood pressure, independently of other Ang II forming enzymes. Whether this effect is dependent on the...
Non-standard Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>Ang</td>
<td>angiotensin</td>
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<tr>
<td>ApoE</td>
<td>apolipoprotein E</td>
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<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
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<td>SNP</td>
<td>single-nucleotide polymorphism</td>
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ApoE genetic background is still unknown. In their mechanistic studies, the authors highlighted the proinflammatory properties of Ang II, particularly increased vascular cell adhesion molecule-1 expression by endothelial cells and enhanced leukocyte adhesion, as important drivers of atherogenesis. However, reduced levels of blood pressure in MMP-8–deficient animals might have significantly contributed to limitation of lesion development, independently of any other Ang II properties. Moreover, the authors have not assessed the direct contribution of MMP-8–mediated Ang II production to the development of atherosclerosis. These issues, as well as the sources of MMP-8 (vascular versus extravascular) that are responsible for MMP-8–dependent Ang II production, blood pressure regulation, and atherosclerosis acceleration, merit further exploration.

Genetic studies have previously broadly reinforced experimental data on the role of specific MMPs in atherosclerosis, by relating functional gene polymorphisms to disease occurrence in humans. The most relevant examples relate to MMP-1, MMP-3, and MMP-9. Thus, in a next important step, Laxton et al investigated the relevance of their experimental findings to the human form of the disease by addressing the relationship between MMP-8 gene variations and both the prevalence and progression of atherosclerosis using DNA samples from 2 different populations. After genotyping 1000 individuals in the first study of patients with coronary artery disease for a panel of 16 single nucleotide polymorphisms (SNPs) consisting of all common SNPs, the authors identified an association between the T allele against carotid atherosclerosis progression and the extent of coronary atherosclerosis. The T allele carried a protective effect, which persisted after adjustment for age, gender, smoking, hypercholesterolemia, hypertension, and diabetes. This might suggest that MMP-8 effects on atherosclerosis could be independent of its effect on the regulation of blood pressure. However, the authors did not directly address the relationship between MMP-8 gene variation and the presence of hypertension, nor did they examine its potential association with circulating levels of Ang II. Importantly, the association between MMP-8 gene variation and atherosclerosis was validated and extended in a second separate cohort of individuals who participated in the Bruneck study, in which the authors identified a protective effect of the T allele against carotid atherosclerosis progression. Taken together, the results support the contention that enhanced MMP-8 activation promotes atherosclerotic lesion growth. However, whether it also promotes plaque complications and the occurrence of acute ischemic syndromes remains unknown.

In summary, Laxton et al have provided important and novel insight into the role of MMP-8 in atherosclerosis. Their data emphasize the need to integrate the numerous and highly relevant matrix-unrelated biological properties of MMPs into every pathophysiological scheme related to disease development, progression, and complications.

Sources of Funding
Supported by Institut National de la Santé et de la Recherche Médicale, France.

Disclosures
None.

References


KEY WORDS: metalloproteinase □ atherosclerosis □ angiotensin □ blood pressure □ adhesion molecules
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Circ Res. 2009;105:827-829
doi: 10.1161/CIRCRESAHA.109.208595
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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