Editorial Comment

Chymase and Matrix Metalloproteinase

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Matrix metalloproteinases (MMPs) are a family of zinc-binding proteases that are capable of degrading extracellular matrix (ECM) during tissue remodeling, including organogenesis, wound healing (1), tumor invasion and angiogenesis (2). MMP-2 (collagenase A) is the major ECM-degrading protease and specifically degrades the basement membrane. Regarding vascular remodeling after balloon injury, MMP-2 is expressed abundantly in restenotic lesions, and the inhibition of MMP-2 by thapsigargin reduces neointima formation (3). In nonhuman primates, MMPs increase with age, and this increase has been positively correlated with the intimal thickening of the carotid artery (4).

Recently, it has been reported that chymase activates several inactive precursors of MMPs (5–7). This finding revealed a new aspect of the function of chymase, in addition to its action as a potent angiotensin II (Ang II)–forming enzyme. It has been reported that chymase produces Ang II (8), which may play a crucial role in coronary artery restenosis. Ang II subtype 1 receptor blocker (ARB) has been proven effective for preventing restenosis after percutaneous coronary angioplasty, but not angiotensin I converting enzyme inhibitor (9, 10). After balloon injury in dog arteries, vascular chymase activity significantly increased and a chymase inhibitor and an ARB were effective in preventing vascular proliferation (11). These studies suggest that chymase-dependent Ang II formation is also harmful in that it promotes the development of vascular hypertrophy in the injured arteries.

In this issue of *Hypertension Research*, Kishi *et al.* (12) report that chymase is involved in the neointimal proliferation after balloon injury in the dog carotid artery. The oral administration of NK3201, a chymase inhibitor, prevented neointimal formation and significantly suppressed both active MMP-2 and chymase activities 2 weeks after balloon injury.

These results suggest that chymase inhibitors can prevent the development of intimal hyperplasia *via* the inhibition of MMP-2 activation in the balloon-injured artery.

Disappointingly, the use of drug-eluting stents has not resulted in a lower rate of adverse events compared to coronary bypass operation, especially in patients with complex lesions or multiple risk factors (13). It has been reported that increased arterial chymase activity is associated with development of atherosclerotic lesions in humans (14), and orally active chymase inhibitor has been shown to reverse this process in high cholesterol–loaded hamsters (15). These data further imply that the clinical application of chymase inhibitor is warranted to prevent atherosclerosis or restenosis after coronary intervention.

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