The rupture of atheromatous plaque causes acute coronary syndrome (ACS) or stroke, which is the leading cause of death worldwide. The features of “vulnerable plaque” are presence of bigger lipid core, accumulation of inflammatory cells, and thinning of fibrous cap. The fibrous cap contains rich fibrillar interstitial collagens, which impart tensile strength, however, are degraded by matrix metalloproteinase (MMP) secreted mainly by plaque macrophages during plaque progression. Among the 23 MMP enzymes, collagenases (MMP-1, 8, 13, and 18) first cleave fibrillar interstitial collagens into fragments, and then, these fragments denature into gelatin, which can be further degraded by gelatinases (MMP-2 and 9). In addition, the tissue inhibitors of metalloproteinases (TIMPs) are endogenous regulators of MMPs. Although TIMP-1 inhibits various MMPs including MMP-1, 3, 7, and 9, TIMP-2 inhibits MMP-2 only. Using gene deletion or overexpression of various MMPs or TIMPs, their role in plaque stability has been studied in apolipoprotein E (apoE) null mice.

Although collagenases consistently promote plaque vulnerability, whether each gelatinase or related protein (MMP-3, TIMP-1, or TIMP-2) is proatherogenic or not remains controversial. Although TIMP-1 inhibits various MMPs including MMP-1, 3, 7, and 9, TIMP-2 inhibits MMP-2 only. In contrast to TIMP-1, TIMP-2 significantly reduced after the 4-day incubation with ARB. As a result, ARB increased gelatinase activity in carotid atheroma supernatant that was examined by zymography. In contrast, ARB reduced MMP-1 and 8 expression in culture supernatant in a previous report.

Clancy et al. suggested that upregulation of gelatinase activity by ARB is one of mechanisms of its plaque stabilization effect. The approach in this report seems to be quite interesting, and this hypothesis is novel. Previously, Sluijter et al. reported that MMP-2 activity increased in stable human carotid plaque, but contrastingly, MMP-9 activity increased in an unstable human carotid plaque. Thus, we should be cautious that two gelatinases (MMP-2 and 9) may differ in terms of their involvement in plaque stability.

Another caution that should be addressed is the time difference between intima formation and macrophage accumulation. In human carotid or coronary artery, diffuse intimal thickening (DIT) composed of

**Key words:** Gelatinase, Matrix metalloproteinase, Plaque, Angiotensin
Table. Effects of gelatinase and TIMPs for plaque stability in ApoE-null mice.

| Gene Manipulation | Site                | Plaque Size | # of SMC | # of Macrophages | Plaque Stability | References        |
|-------------------|---------------------|-------------|----------|------------------|-----------------|-------------------|
| MMP-2 null        | aortic sinus, Ao    | ↓           | ↓        | →                | ↓               | Kuzuya et al. (2006) |
| MMP-3 null        | Ao                  | ↑           | N/D      | ←                | ↑               | Silence et al (2001) |
|                   | BCA                 | ↑           | ↓        | →                | ↓               | Johnson et al. (2005) |
| MMP-9 null        | Ao, BCA             | ↓           | N/D      | ↓                | ↑               | Luttun et al (2004) |
|                   | Ao, BCA             | ↑           | ↓        | ↑                | ↓               | Johnson et al. (2005) |
|                   | carotid ligation    | ↓           | ↓        | ↓                | N/D             | Choi et al. (2005)  |
| MMP-9 O/E         | Ao                  | →           | →        | →                | →               | Gough et al. (2006) |
|                   | Ao                  | →           | →        | →                | →               | de Nooijer et al. (2006) |
| active MMP-9 O/E  | BCA                 | →           | N/D      | →                | ↓               | Gough et al. (2006) |
| TIMP-1 null       | aortic sinus, Ao    | →           | →        | →                | →               | Lemaître et al. (2003) |
|                   | aortic sinus, Ao    | ↓           | N/D      | ↑                | ↓               | Silence et al (2002) |
|                   | BCA                 | →           | ↓        | →                | →               | DiGregoli et al. (2016) |
| TIMP-1 O/E        | Ao                  | ↓           | N/D      | ↓                | ↑               | Rouis et al. (1999) |
|                   | BCA                 | →           | →        | →                | →               | Johnson et al. (2006) |
| TIMP-2 null       | BCA                 | →           | ↓        | ↑                | ↓               | DiGregoli et al. (2016) |
| TIMP-1 O/E        | BCA                 | →           | ↑        | ↑                | ↑               | Johnson et al. (2006) |

Increases (↑), decreases (↓) or no change (→). Abbreviations; O/E: overexpression, Ao: aorta, BCA: brachiocephalic artery, N/D: no data. This table is modified from Ref. 3, originally published by Newby AC in Vascul Pharmacol, 2012

VSMC is developed first in adolescence, and then, macrophages accumulate into the intima later. In contrast, accumulation of VSMC and macrophages into the intima occur almost at the same time in ApoE null mice. Although gelatinase gene deletion causes vulnerable plaque in ApoE null mice, whether gelatinase inhibition results in destabilization of human atherosomatous plaque is unclear. We have recently developed a rabbit model whose time course from DIT, a stable plaque, to unstable plaque is similar to that of a human⁸. ARB administration in this rabbit revealed that gelatinase activity in the plaque examined by zymography did not change⁹. Which mechanism, i.e., reduced collagenase expression (enzyme activity has not been examined) or upregulation of gelatinase activity⁵, is mainly involved in ARB’s plaque stable effect remains unknown in human carotid plaque.

Lastly, the dominant mechanism of ACS or stroke may change in the ‘statin era’ from plaque rupture to plaque erosion as recently pointed out by Libby et al¹⁰. Long-term statin treatment has already begun to modify plaque geometry, suggesting that plaque erosion induced by non-fibrillar collagen breakdown or endothelial cell apoptosis may increase due to ACS or stroke. How the MMP–TIMP system is involved in plaque erosion may be under focus in the near future as it is presently unknown. The article by Clancy et al. is very much suggestive from these points of views, and further studies are expected in this regard.

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