Editorial Comment

Inhibition of Matrix Metalloproteinase and Hypertension

Takafumi OKURA[1)] and Jitsuo HIGAKI[1)]

(*Hypertens Res* 2007; 30: 477–478)

***Key Words*: matrix metalloproteinases (MMPs), natural tissue inhibitors of MMP (TIMP)-3, hypertension, N^{ω}-nitro-L-arginine methyl ester, a disintegrin and metalloproteinase (ADAM)17**

Matrix metalloproteinases (MMPs) are zinc-endopeptidases involved in numerous physiological and pathological processes. MMPs play roles in tissue growth, angiogenesis, cell migration, inflammation, wound healing, cardiovascular disease, cancer and metastasis (*1*). The natural tissue inhibitors of MMPs (TIMPs) are a family of inhibitors capable of regulating MMP activity (*2*). The four members have many similarities and overlapping specificities, but their biological properties and local expression patterns exhibit distinctive features.

TIMP-3 is the only TIMP that binds to the extracellular matrix by its interaction with chondroitin sulfate and heparan sulfate (*3*). Furthermore, TIMP-3 contains an amino acid sequence required to inhibit a disintegrin and metalloproteinase (ADAM)17, also called tumor necrosis factor (TNF)-α converting enzyme (TACE) (*4*). ADAM17 is responsible for the release of several transmembrane proteins, including neuregulins 1 and 2, fractalkine, and TNF-α (*5*).

In this issue of *Hypertension Research*, Higuchi *et al*. report that TIMP-3 deficiency inhibited blood pressure elevation and myocardial microvascular remodeling induced by chronic administration of N^{ω}-nitro-L-arginine methyl ester (L-NAME) (*6*). Chronic administration of L-NAME induced hypertension and increased the wall-to-lumen ratio and perivascular fibrosis. Mice deficient in TIMP-3 gene expression showed a partial reduction in these L-NAME–induced phenomena. Furthermore, Higuchi *et al*. (*6*) showed that L-NAME–induced production of reactive oxygen species (ROS) in cardiac microvessels was lower in TIMP-3 knockout mice than wild type mice. These findings constitute new evidence of a direct association between MMP-related molecules and hypertension.

Numerous reports have shown the pathophysiological importance of MMPs and TIMPs in cardiovascular diseases, such as heart failure, myocardial infarction, stroke, aortic aneurysm and aortitis syndrome. However, there have been few reports examining the relationship between MMP/TIMP and hypertension. The serum concentration and roles of MMP or TIMP in hypertensive patients are controversial. Those reports that are available show conflicting results in regard to the serum concentration and roles of MMP and TIMP in hypertension.

The fact that MMP/TIMP is involved in the pathophysiology of L-NAME–induced hypertension and organ damage is quite interesting. To understand why TIMP-3 deficiency influences L-NAME–induced hypertension and organ damage would be more interesting, since TIMP-3 has unique functions other than inhibition of MMPs. For example, overexpression of TIMP-3 induces apoptosis in vascular smooth muscle cells but not endothelial cells (*7*). This unique ability makes TIMP-3 particularly suitable as a potent inhibitor of restenosis after coronary intervention. Johnson *et al*. reported that stent-based delivery of TIMP-3 adenovirus inhibited neointimal formation in porcine coronary arteries (*8*).

TIMP-3 inhibits the activity of ADAMs, including ADAM10, 12, 17, and 19. ADAM17 (TACE) can alter the availability of TNF-α by cleaving it from myeloid and T cells, allowing the shed molecules to diffuse and act on the surrounding tissue and vasculature, as well as at distant sites. Thus the regulation of ADAM17 is an important check point

From the [1)]Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Toon, Japan.

Address for Reprints: Takafumi Okura, M.D., Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Toon 791–0295, Japan. E-mail: okura@m.ehime-u.ac.jp

Received March 7, 2007.

for the magnitude of an inflammatory response (*9*). ADAM17 activity might be related to the reactive oxygen species generation in TIMP-3 deficient mice. Finally, TIMP-3 deficiency or MMP activation might reduce the activation of the renin-angiotensin system (RAS), which was recently reported to play a role in L-NAME–induced hypertension and organ damage by promoting oxidative stress (*10*).

In conclusion, the paper of Higuchi *et al*. (*6*) suggests that inhibition of TIMP-3 may be a promising new strategy for the treatment of hypertension and target organ damage.

References

1. Visse R, Nagase H: Matrix metalloproteinase and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res* 2003; **92**: 827–839.
2. Brew K, Dinakarpandian D, Nagase H: Tissue inhibitors of metalloproteinases: evolution, structure and function. *Biochim Biophys Acta* 2000; **1477**: 267–283.
3. Yu WHS, Yu S, Meng Q, *et al*: TIMP-3 binds to sulfated glycosaminoglycans of the extracellular matrix. *J Biol Chem* 2000; **275**: 31226–31232.
4. Black RA, Rauch CT, Kozlosky CJ, *et al*: A metalloproteinase disintegrin that releases tumor necrosis factor-α from cells. *Nature* 1997; **385**: 729–733.
5. Singh RJR, Mason JC, Lidington EA, *et al*: Cytokine stimulated vascular cell adhesion molecules-1 (VCAM-1) ectomain release is regulated by TIMP-3. *Cardiovasc Res* 2005; **67**: 39–49.
6. Higuchi M, Yasuda O, Kawamoto H, *et al*: Tissue inhibitor of metalloproteinase-3 deficiency inhibits blood pressure elevation and myocardial microvascular remodeling induced by chronic administration of N^{ω}-nitro-L-arginine methyl ester in mice. *Hypertens Res* 2007; **30**: 563–571.
7. Baker AH, Zaltsman AB, George SJ, *et al*: Divergent effects of tissue inhibitor of metalloporteinase-1, -2, or -3 overexpression on rat vascular smooth muscle cell invasion, proliferation, and death *in vitro*. TIMP-3 promotes apoptosis. *J Clin Invest* 1998; **101**: 1478–1487.
8. Johnson TW, Wu YX, Herdeg C, *et al*: Stent-based derivery of tissue inhibitor of metalloproteinase-3 adenovirus inhibits neointimal formation in porcine coronary arteries. *Arterioscler Thromb Vasc Biol* 2005; **25**: 754–759.
9. Smookler DS, Mohammed FF, Kassiri Z, *et al*: Tissue inhibitor of metalloproteinase 3 regulates TNF-dependent systemic inflammation. *J Immunol* 2006; **176**: 721–725.
10. Ishiguro K, Sasamura H, Sakamaki Y, *et al*: Developmental activity of the renin-angiotensin system during the "critical period" modulates later L-NAME–induced hypertension and renal injury. *Hypertens Res* 2007; **30**: 63–76.