CLINICAL IMPLICATIONS OF BASIC RESEARCH

Regression of Aortic Aneurysms through Pharmacologic Therapy?

Subodh Verma, M.D., Ph.D., and Thomas F. Lindsay, M.D., C.M.

“There is no disease more conducive to clinical humility than aneurysm of the aorta.” These words of Sir William Osler still resonate today, when many patients with ruptured abdominal aortic aneurysms die before reaching the hospital and the mortality rate among those who reach the hospital can exceed 50 percent. The prevention of rupture through early detection and elective repair remains the standard therapy. A recent study by Yoshimura et al.,¹ however, suggests the possibility of pharmacologic therapy.

Researchers have found that the degradation of the extracellular-matrix proteins elastin and collagen in the aortic wall is critical to the pathogenesis of aortic aneurysms.² Specifically, the matrix metalloproteinases 2, 8, and 9 that degrade the extracellular matrix have been implicated. Oxidative stress, chronic medial and adventitial inflammation, and genetic influences are other important factors. The loss of elastin in the aortic wall is associated with dilatation, and the loss of collagen promotes rupture.

Yoshimura et al. showed that a stress-activated protein kinase, Jun N-terminal kinase (JNK), is critical to the development of abdominal aortic aneurysms in two mouse models (Fig. 1). JNK, which mediates a variety of signaling pathways involved in inflammation, has not been previously implicated in the pathogenesis of aortic aneurysms. JNK activates inflammatory cytokines in vascular smooth-muscle cells. It also regulates the genes involved in the biosynthesis and degradation of the extracellular matrix, a role underscored by the results of gene-expression profiling by Yoshimura et al. Furthermore, the authors showed that tissues from abdominal aortic aneurysms in humans coexpressed matrix metalloproteinase 9 and activated JNK and that a JNK

inhibitor, SP600125, repressed the release of matrix metalloproteinases 9 and 2.

In vitro data are all very well, but the real interest lies, of course, in the effect of JNK inhibition in vivo. In this area, the results of Yoshimura et al. are impressive. The authors showed that treatment with SP600125 prevented the development of abdominal aortic aneurysms in two mouse models. This treatment almost completely prevented aortic dilatation and medial thinning yet preserved the integrity of the elastic lamellae. The authors also showed that JNK facilitates the degradation of tissue in abdominal aortic aneurysms by suppressing the formation of the extracellular matrix. It seems, therefore, that inhibiting JNK with the use of SP600125 may reverse the progressive destruction of the extracellular matrix and thereby prevent the dilatation that can lead to aneurysm. This surprising regression of aortic dilatation suggests that the repair and stabilization of the extracellular matrix can be achieved by pharmacologic intervention.

Whether such therapy will limit the rupture of aortic aneurysms or impose deleterious effects on other cellular processes remains to be tested. The successful treatment of other animal models of aneurysm formation with SP600125 or another JNK inhibitor would strengthen the conclusions of Yoshimura et al.

Aneurysm rupture is associated with areas of peak stress in the aortic wall, and levels of the matrix metalloproteinases 8 and 9 at the rupture site are markedly elevated, as compared with the intact portion of the same aorta.^{3,4} These findings suggest that a localized imbalance in the homeostasis of the extracellular matrix may be responsible for aortic aneurysm rupture. A pharmacologic approach that targets both matrix me-

tallopoteinases and JNK could result in the regression of aortic aneurysms and confer resistance to aortic rupture.

No potential conflict of interest relevant to this article was reported.

From the University of Toronto, Toronto.

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4. Wilson WR, Anderton M, Schwalbe EC, et al. Matrix metalloproteinase-8 and -9 are increased at the site of abdominal aortic aneurysm rupture. *Circulation* 2006;113:438-45.

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CORRECTION

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Regression of Aortic Aneurysms through Pharmacologic Therapy? . On page 2068, in Figure 1, "Collagen layer" should have been labeled "Fenestrated elastic lamella," and the collagen bundles should have been shown lying on the elastin fibers and not so closely attached to the smooth-muscle cells. Also, the smooth-muscle cells should have been oriented in a parallel fashion, not in a perpendicular fashion as shown. Smooth-muscle cells should have been shown attached to elastin by fibers containing elastin and other types of fibers.

The figure has been corrected on the *Journal's* Web site at www.nejm.org.