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EDITORIAL COMMENT

Biologically-Based Therapies for Aortic Diseases

Why the Long Lag in Translation?*

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Aortic diseases seem to have a "stepchild" status in contemporary cardiovascular medicine. We understand well many risk factors for aortic aneurysmal disease, aortic dissection, and aortic occlusive disease (**Figure 1**). Moreover, biological insights into the pathogenesis of these aortic diseases (not to mention aortic valve disease) have burgeoned. We have identified genetic causes of numerous aortic diseases (1). Examples include fibrillin defects in Marfan syndrome, mutations in the transforming growth factor-beta signaling pathways in Loeys-dietz syndrome, as well as variants in NOTCH1 and ACTA2 in the bicuspid valve aortopathy complex.

Decades of research have underscored abnormalities in extracellular matrix metabolism in abdominal aortic aneurysmal disease (2–4). Diseased aortae display increased expression of matrix metalloproteinases that can degrade aortic elastin, as well as elastinolytic enzymes of the cysteinyl proteinase cathepsin family (5). Aortic aneurysms also have dysregulation of the endogenous inhibitors of these matrix-degrading enzymes including the tissue inhibitors of matrix metalloproteinases and cystatins (6–9). Many animal experiments have implicated disordered cytokine signaling and proteinase/proteinase inhibitor imbalance in the pathogenesis of experimental aortic aneurysms (3,10,11).

The work reported by Andreata et al. (12) in this issue of the *Journal* represents another step in understanding the biology of aortic disease and provides a potential novel therapeutic avenue to management (12). The investigators used an agonist peptide for a cell surface structure, known as CD31, as a biological probe and as a potential therapy for experimental dissecting aortic aneurysms. Cells such as the endothelium and platelets express CD31 on their surface. Homophilic interactions between CD31 on neighboring cells prove anti-inflammatory and can mute immune responses. This investigative team developed an agonist peptide that has some promising properties for clinical translation, including having undergone toxicity and pharmacokinetic characterization. The investigators induced dissecting aortic aneurysms in atherosclerotic mice using a widely adopted experimental preparation: the chronic infusion of angiotensin II.

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They found that administration of the CD31 agonist peptide forestalled the formation of aneurysms and enhanced the resolution of intramural hematomas and the deposition of a collagenous extracellular matrix at the site of aortic dissections. These beneficial effects associated with an increased slant toward macrophages with functions associated with repair and muting of inflammation. Studies on human aortic disease specimens affirmed the clinical relevance of their experimental results. Concordant with the observations in mice, specimens of human aortas obtained during the healing phase of dissection showed scant expression of CD31 on macrophages, but enhanced expression of markers of inflammatory activation.

The authors used a therapeutic peptide comprised of D-amino acids as a CD31 agonist. Such peptides that contain the D-enantiomers of amino acids generally evade the usual pathways for elimination (natural peptides contain L-amino acids). Thus, these peptides

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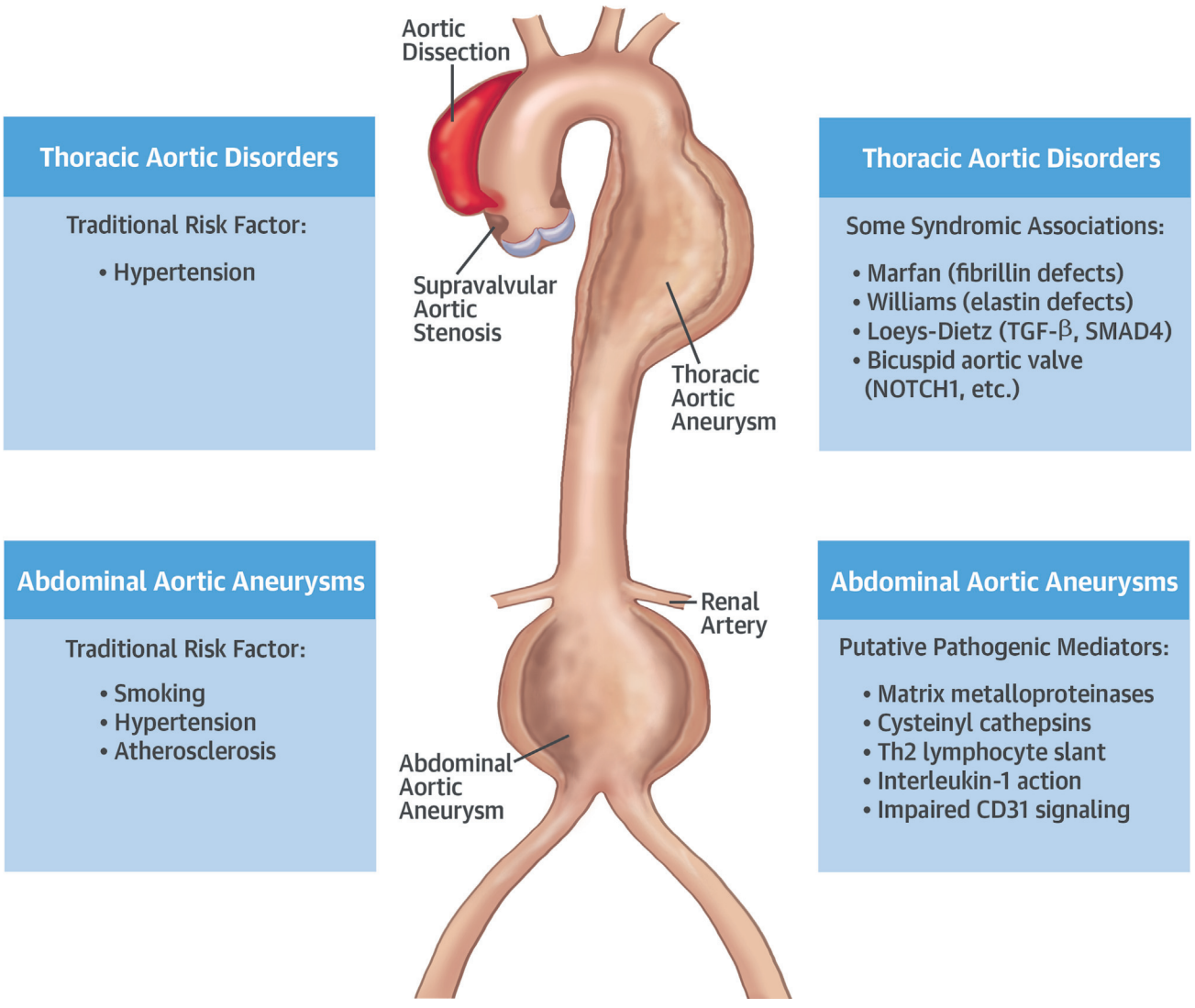
FIGURE 1 Risk Factors for Aortic Diseases and Biological Pathways Implicated in Their Pathogenesis



The figure depicts the aorta with a dissection in the thoracic portion and an infrarenal abdominal aortic aneurysm distally. **(Left)** List of certain common risk factors associated with these aortic diseases. **(Right)** List of examples of fundamental biological pathways implicated in these aortic diseases. Although we can address several of the modifiable risk factors for these aortic diseases, and we have considerable biological insight into their pathogenesis, biologically-directed therapies for these conditions have lagged considerably compared with other cardiovascular conditions. CD31 = cluster of differentiation 31; SMAD4 = Mothers against decapentaplegic homolog 4; TGF = transforming growth factor; Th2 = T helper 2 cells.

might accumulate with chronic administration. Yet, limited exposure might avoid build-up of unmetabolized drug.

Although proinflammatory T cells (Th1 lymphocytes) can produce the proinflammatory cytokine interferon gamma that activates proinflammatory functions of macrophages (13), abdominal aortic aneurysms actually display a predominance of Th2 lymphocytes (14). The Th2 cells may, however, elaborate interleukin-4 that can increase production of elastinolytic enzymes (15). Thus, the results obtained experimentally with aortic dissection may not necessarily apply to abdominal aortic aneurysms.

There is increasing appreciation of the role of resident macrophages in cardiovascular and other tissues (16). It would be interesting to know whether the proinflammatory macrophage subset these workers localized in dissecting aneurysms in mice arose from infiltrating mononuclear phagocytes or from those resident in aortic tissue.