Diseases of the aorta, primarily aneurysms and dissections, are the 14th leading cause of death in the United States. Abdominal aortic aneurysms (AAAs) are responsible for >80% of all aortic aneurysms, with >100,000 AAA repairs performed in the US between 1988 and 2000. The risk factor profile of patients with AAAs has been well described. This is a disease primarily of older adults, with white men much more likely to harbor an AAA than are black women. Other risk factors for developing an AAA include cigarette smoking, hypertension, chronic obstructive pulmonary disease, and a family history of aortic aneurysms. Atherosclerosis in other vascular beds also puts the patient at increased risk for the development of an aortic aneurysm.

During the past 20 years, an explosion of information on the pathogenesis of aortic aneurysms has been generated. Much of this basic science work has been descriptive and performed by surgeons, who are the primary managers of the treatment of patients with AAAs. This occurred at least partially because there is no proven medical therapy to inhibit aortic aneurysms from forming or slowing their growth once a small AAA has been recognized. Therefore, the management of AAAs is surgical, with intervention occurring once the risk of aortic rupture exceeds the risk of elective repair.

There are 2 surgical options for patients with an AAA once their aneurysm has attained a certain diameter based on 2 large randomized trials. Open surgical repair has been established for >50 years and is a curative procedure. This cure comes with an increased short-term morbidity and mortality as compared with the less-invasive option of endovascular repair. Endovascular AAA repair, although associated with lower morbidity and mortality as compared with open AAA repair, converts the AAA into a chronic condition that needs to be followed expectantly with serial CT scans. Reintervention is required if the AAA continues to enlarge or if the endograft structurally deteriorates. Ongoing trials in the United States and Europe will determine whether endovascular therapy should be the primary therapy offered to patients once their AAA reaches a threshold diameter.

Unfortunately, this leaves a large cadre of patients (10% of men older than age 65 may harbor an AAA) without any good medical options to treat their AAA. Clearly, smoking cessation is indicated, but rarely successful. In addition, although β-blockers have been touted in animal studies as being capable of slowing AAA growth, the best study to date in humans with AAAs failed to show a significant reduction in AAA growth rates as compared with placebo.

Pharmacological therapy using doxycycline, a nonselective matrix metalloproteinase inhibitor, has been the most well-studied compound in the treatment of AAAs. In rodents, systemic and periarterial application of doxycycline inhibits AAA growth. Studies in humans also suggest that doxycycline may slow AAA growth.

Although there is a paucity of studies, even in rodents and mice, that have documented inhibition of AAA growth rates, the present study by Dai et al documents convincingly aortic aneurysm “healing.” This concept represents the Holy Grail to aneurysm researchers. The idea that a researcher could take “burned out” rodent and human aneurysms and cause resident cells to develop synthetic function capable of creating an environment where the balance between proteolysis and repair favors tissue repair is remarkable.

In the present article, the role of transforming growth factor-β1 (TGF-β1) in preventing aneurysm formation and growth is explored. This multipotent cytokine appears to be an excellent “target” because it is known to induce the expression of fibrillar collagen and elastin. In addition, TGF-β1 also is known to downregulate inflammation and MMP expression, both critical during AAA formation. In earlier studies, the authors documented aneurysm stabilization in the xenotransplant AAA model using endovascular smooth muscle cell (SMC) therapy. Importantly, endovascular SMC therapy was associated with an increase in the expression of TGF-β1, not TGF-β2 or TGF-β3. The Dai et al article is therefore a natural extension of this earlier observation with well-accepted gene therapy techniques.

I must temper my enthusiasm for these results with my continued skepticism about the use of gene therapy to accomplish this goal in humans with AAAs. At present, gene therapy, especially with viral vectors, is delivery of a single gene in a single setting (most often before the insulting event). In cardiovascular disease in particular, the list of basic science studies with gene therapy is exhaustive. Almost all studies inhibit whatever process (e.g., intimal hyperplasia, stent restenosis, atherosclerosis) they are intended to, with only a single gene being targeted or inhibited. Unfortunately,
to date, the use of gene therapy in humans almost uniformly has yielded negative results.

In the Discussion, Dai et al acknowledge that transgene expression of TGF-β1 is exhausted by 28 days, yet TGF-β1 acts as a “self-promoting” cytokine in the aneurysm wall, and increased endogenous synthesis occurs even after delivered gene expression is exhausted. The authors conclude that “time-limited” expression of TGF-β1 may be sufficient for AAA stabilization. The eventual role of adenoviral transfection of TGF-β1 as a therapeutic agent in the treatment of human AAAs remains to be seen; however, the goal and an appropriate target (TGF-β1) appear to have been identified.

Although I applaud the goal (aneurysm healing), I suggest that the authors in earlier works began to develop a strategy that seems more appealing and practical. In an earlier publication, Allaire and coauthors used syngeneic vascular smooth muscle cells in the xenotransplant aneurysm model and documented the stabilization of aneurysm diameter, blockage of extracellular matrix degradation, and regeneration of the diseased vessel wall. In a manner similar to the present investigation, aneurysm healing was performed by altering the balance of vessel wall remodeling with increased tissue inhibitors of metalloproteinases and decreased matrix metalloproteinases. The authors concluded that whether this type of strategy may be applied to humans “needs further investigation.” I agree with the authors that now is the time for expanding the application of this type of technology.

References


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Gene Therapy to Treat Aortic Aneurysms: Right Goal, Wrong Strategy
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