Tilting at the tilted protease balance in arterial aneurysmal disease

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This editorial refers to 'Gingival fibroblasts protect against experimental abdominal aortic aneurysm development and rupture through TIMP-1 production' by A. Giraud et al., pp. 1364–1375.

The prevention and treatment of aortic aneurysms present a persistent clinical challenge. While the prevalence of abdominal aortic aneurysms (AAAs) should decrease in light of reduced cigarette smoking, the aging of the population may counterbalance the salutary effect of receding tobacco abuse. Thoracic aortic aneurysms often result from syndromic genetic abnormalities and/or uncontrolled hypertension. AAAs associate with classical atherosclerotic risk factors, in particular male sex, cigarette smoking, and hypertension. The treatments for aortic aneurysm disease involve invasive procedures: open repair or endovascular stent grafting. Given the frequent comorbidities in the affected population, surgical repair entails considerable risk, as well as requiring prolonged recovery and expenditure of health care resources. Endovascular repair, while less invasive than open surgery, presents technical placement limitations and post-operative complications including device migration, occasional iliac limb thrombosis, and the persistent problem of ‘endoleaks’ with late rupture. Not all patients who present with AAA have anatomy suitable for endovascular repair. Medical therapy for AAA remains a major unmet need. Hence the importance of understanding the pathophysiology of aneurysm formation and the development of novel and less invasive strategies for its management.

Transmural destruction of normal arterial architecture characterizes late-stage aneurysms (Figure 1). In particular, human AAAs display fragmentation or the absence of the over 20 ordered elastic laminae that characterize the normal tunica media of large arteries, in addition to the accumulation of inflammatory cells. Mediators elaborated by the inflammatory cells may trigger death by apoptosis of smooth muscle cells, the source of the bulk of arterial extracellular matrix, including elastin. Given the prominence of abnormalities in elastin content, many investigators have focused on elastolysis as a key pathogenic process in aneurysm formation. Initial work focused on overexpression of matrix metalloproteinases (MMPs), some of which exhibit considerable elastase activity (e.g. MMP-9 and MMP-12).²

Twenty years ago our group hypothesized that an imbalance between MMPs and their endogenous inhibitors, the tissue inhibitors of matrix metalloproteinases (TIMPs), could prevail in aneurysmal disease and account for excess elastin degradation.³ Analyses of human aneurysmal tissue that substantiated this hypothesis by showing increased MMPs and reduced TIMPs.⁴ Cytokines elaborated by T-helper-2 lymphocytes signal MMP-12 production in experimental AAA.⁵ In addition to metalloelastases, granulocytes contain serine proteinases including neutrophil elastase and cathepsin G, and mast cells also produce the serine proteinases chymase and trypstatine. These serine proteinases (save for neutrophil elastase) may not have direct elastolytic activity, yet can aggravate experimental aneurysm genesis.⁶ Moreover, the potent cysteine elastases cathepsins S, K, and L contribute to human and experimental AAA.⁷–⁹ A tilted balance between these cysteine elastases over their endogenous inhibitor, cystatin C, prevails in aneurysmal disease as well as atherosclerosis.¹⁰

These various lines of evidence provide strong support for the notion that an imbalance between elastolytic enzymes and their inhibitors contribute to the pathogenesis of aortic aneurysms (Figure 1). Thus, elastases have emerged as an attractive therapeutic target in the treatment of AAA. Clinical trials to date with the weak MMP inhibitor doxycycline, however, have not shown clear benefit in forestalling the growth of AAA, although the Non-invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TAACT) continues.¹¹ Giraud et al.¹² have taken an innovative approach: using cell therapy to stall the evolution of experimental AAAs in mice. For a variety of rational reasons, they have used gingival fibroblasts as a source of cells for local transfer to the abluminal periadventitial region. This treatment fostered preservation of the elastic laminae and reduced the risk of AAA expansion and rupture. The study authors provide convincing evidence, using cells from genetically modified mice, that provision of the endogenous MMP inhibitor TIMP-1 accounts for the protection against aneurysm disease. These investigators did not evaluate the other TIMPs (2–4) implicated in the regulation of MMP activity in arterial lesions.¹³,¹⁴ These important in vivo results illustrate the fundamental importance of dysregulation of the balance between elastases and anti-elastase in AAA pathogenesis (Figure 1). They also illustrate a novel therapeutic avenue for treating these lesions.

These mouse experiments used an open surgical approach to introduce the gingival fibroblasts after expansion in vitro. In humans, obtaining

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autologous gingival fibroblasts and their multiplication in culture might present a barrier to translation. Perhaps a combination of endovascular stent-graft deployment and cell transfer might provide a two-pronged approach to a nonsurgical treatment for AAAs that require intervention. Additionally, with recent advances in imaging, percutaneous delivery methods may emerge as reasonable strategies to deliver the cell therapy. The authors delivered the gingival fibroblasts simultaneously with the elastase injury or within a week in angiotensin II-induced experimental aneurysms. Thus, the current report does not define temporal therapeutic windows, an important consideration as this approach moves toward translation. Nonetheless, the results of Giraud et al.11 not only provide an in vivo affirmation of hypotheses generated long ago by observations on human tissues5 but also point to a new pathway for therapy of AAA.

Yet, a number of questions remain unanswered with regard to the prevalent problem of aortic aneurysmal disease. What trigger or triggers instigate the inflammation that appears to provoke the proteolytic pivot in the pathogenesis of AAA? Why does atherosclerosis manifest itself so differently in the large elastic arteries such as the abdominal aorta, where it typically causes ectasia, while the smaller arteries such as those supplying the heart, the lower limbs, and brain more often develop flow-limiting stenosis or lesions that cause occlusive thrombi? Does this dimorphic expression of the disease arise because of architectural differences, distinct embryologic origins of the constituent smooth muscle cells, hydrodynamic variables, or other mechanisms? These questions furnish a fertile field for future research. In the meantime, we should redouble our efforts to curtail cigarette smoking and intensify treatment of atherosclerotic risk factors to prevent the consequences of arterial diseases, be they expansive or constrictive.

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References


