Aneurysm prevention: keep the cat out of the bag

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This editorial refers to ‘Deficiency of cathepsin S attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein E-deficient mice’ by Y. Qin et al., pp. 401–410, this issue.

In this issue of Cardiovascular Research, Qin et al.¹ show that the incidence of abdominal aortic aneurysm formation in apolipoprotein E (apo E) knockout mice is profoundly inhibited if the mice are additionally deficient in cathepsin S, an elastinolytic cysteine proteinase.

Cathepsin S, traditionally thought of as a lysosomal proteinase involved only in the terminal degradation of endocytosed proteins, is now known to be active in the cytosol, the nucleus, and the extracellular matrix and to play a number of diverse cell-specific roles, including the destruction of extracellular matrix collagen and elastin and weakening of the arterial wall.²³ Some cells can also release cathepsin S in a regulated manner to facilitate their migration and, in the case of endothelial cells, to allow new blood vessels to invade tissue. An elegant study by Abdul-Hussien et al.⁴ identified cathepsin S as the most highly up-regulated proteinase in abdominal aortic aneurysms: cathepsin K was up-regulated to a much lesser extent and its deletion was subsequently shown to have no effect on aneurysm development in mice.⁵ Cathepsin S is therefore an obvious therapeutic target, and, as Qin et al. have demonstrated, its removal is an effective way of preventing aneurysm development in an experimental model.

Cathepsin S plays a central role in antigen processing by degrading the invariant chain (Ii) from the MHC class II–Ii complex within the endosomal compartment of antigen-presenting cells, thus controlling antigen presentation to CD4⁺ T-cells.⁶ Cathepsin S inhibitors are currently being trialled in diseases with an autoimmune component, such as rheumatoid arthritis, multiple sclerosis, and psoriasis.⁷ There is evidence of features of autoimmunity in abdominal aortic aneurysms; thus, a decrease in antigen presentation to CD4⁺ T-cells could also have contributed to the beneficial effects seen in the study of Qin et al., since the authors reported a significant reduction in CD4⁺ T-cells in the animals lacking cathepsin S.

Qin et al.⁸ used a well-established experimental model of aneurysm formation in which apo E knockout mice are treated with angiotensin II by continuous subcutaneous infusion for 28 days. The aneurysms that form in the abdominal aorta are grossly dilated into bag-like structures and are characterized by breaks in the medial elastin layers. In the study of Qin et al., cat S/apo E double knockouts had fewer elastin breaks in the media, findings which are consistent with recent reports that pharmacological inhibition of cathepsin S reduces atherosclerotic medial elastin breakdown in apo E knockout mice⁹ and that the deletion of an endogenous inhibitor of cysteine proteinases, cystatin C, causes an increase in the number of such breaks.¹⁰ Since angiotensin II infusion does not cause similar changes in elastin stability in wild-type mice, it is reasonable to speculate that arterial elastin might be particularly vulnerable in apo E knockouts and that angiotensin II infusion exacerbates this vulnerability. One possible mechanism for this is up-regulation of cathepsin S activity by angiotensin via the AT1 receptor,¹¹ a picture seen in a range of other cardiovascular pathologies.¹²–¹⁵

Animal models in which a chronic disease is interrogated at a single fixed point in time suffer from the problem that a change in the rate of the development of the disease can manifest, spuriously, as a change in disease severity. For example, if aneurysm development were slowed by the deletion of cathepsin S, the degree of dilatation in the abdominal aorta might be reduced in the double knockout mice at the time point used in the study, but unaffected at later times because of the phenomenon of ‘catch-up’. Interventions that slow the development of chronic disease but do not affect its eventual severity are unlikely to be clinically useful, so it is important to try to determine precisely which effect is being produced.

This is not merely a theoretical concern because there is some evidence that cathepsin S can influence the rate of the development of murine atherosclerosis. Cathepsin S/low-density lipoprotein (LDL) receptor double knockout mice show impaired atherogenesis compared with LDL receptor single knockout controls.¹⁶ Feeding an atherogenic diet for 12 weeks to the double knockouts resulted in an average lesion severity similar to that seen in single knockout controls after just 8 weeks of feeding, and 26 weeks of atherogenic diet feeding in the double knockouts produced lesions similar to those observed after 12 weeks in the single knockouts. This suggests that cathepsin S could be involved in the rate of the progression of atherosclerotic lesions¹⁷ and therefore might be exerting a similar effect in aortic aneurysm. This hypothesis could be tested in two main ways. First, later time points could be examined in the angiotensin II-treated cathepsin S/apo E double knockouts to see if aneurysm size continues to develop beyond 28 days, to determine whether it reaches the point where it equals the picture seen in controls. Secondly, a cathepsin S...
inhibitor drug could be used to treat apo E knockout mice starting at a time after the initiation of angiotensin II infusion and when aeurysms are already developing. If treated animals still showed reduced aeurysm development under these conditions, this would be reasonable evidence that cathepsin S plays a fundamental role in aeurysm pathology rather than just a permissive one in aeurysm initiation.

An important observation by Qin et al. was a reduction in smooth muscle cell apoptosis in animals lacking cathepsin S. Apoptosis can be triggered by the loss of integrity of the lysosomal membrane with subsequent release of cathepsins into the cytosol. Cathepsin S is likely to be the most active of the lysosomal cathepsins within the cytosol due to its greater stability at neutral pH. The extent to which smooth muscle cell apoptosis in angiotensin II-treated mice reflects the situation in humans with aortic aeurysms is not known, but preventing the loss of these cells should be beneficial for arterial wall strength and integrity. In this respect, it is interesting that cathepsin S deletion increased aortic smooth muscle cell resistance to the anti-oxidant, and sometimes pro-apoptotic, agent pyrrolidine dithiocarbamate in vitro. In future studies, a more physiologically relevant oxidant should also be investigated.

In summary, Qin et al. have taken an important first step towards establishing cathepsin S as a credible therapeutic target in abdominal aortic aeurysm. In other words, they have shown the importance of keeping the cat out of the bag.

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References