Cathepsin Enzymes and Cystatin C: Do They Play a Role in Positive Arterial Remodeling?

To the Editor:

We have read the impressive article recently published by Aoki et al.1 evaluating the cathepsin enzyme system in cerebral aneurysm formation. By using quantitative RT-PCR and immunohistochemistry, the authors have demonstrated increased expression of cathepsin B, cathepsin K, and cathepsin S in arterial wall of the cerebral aneurysms, whereas the expression of cystatin C was found to be decreased. These findings suggest an imbalance between cysteine cathepsins and their inhibitor. This imbalance may cause the excessive breakdown of extracellular matrix in the arterial wall resulting in progressing arterial aneurysm formation. This conclusion was supported by the experimental use of the cathepsin inhibitor NC-2300.

Cystatin C is a ubiquitously expressed, secretory protein that inactivates members of the cathepsin family of cysteine proteases, and subsequently plays a role in protein catabolism, antigen presentation, bone resorption, hormone processing, and which couples to cleavage of membrane and extracellular matrix proteins during tissue remodeling.2–4 The role of cystatin C in cardiovascular diseases has gained an interest in recent years. Although some studies have reported decreased expression of cystatin C in atherosclerotic lesions and increased atherosclerosis in the absence of cystatin C,5–7 there is growing evidence that the reduction or inhibition in cystatin C expression correlates with dilating vascular disease. These vascular dilatations, namely coronary artery ectasia, abdominal aortic aneurysm or cerebral artery aneurysm can be regarded as positive arterial remodeling which are associated with the enlargement of the external elastic laminae of the corresponding vessel walls.

Recently, decreased cystatin C levels have been shown in patients with coronary artery ectasia coexisting with obstructive coronary artery disease, when compared to patients with coronary artery disease alone.8 Moreover, patients with abdominal aortic aneurysm were shown to have higher levels of cathepsin enzyme activity and lower levels of cystatin C as compared to patients with obstructive abdominal aortic disease.9 These data suggest that cystatin C positively correlates with obstructive atherosclerotic disease.9

It has already been demonstrated that dilated vascular segments are often not localized to a single vascular territory. Increased, several dilating vascular diseases such as abdominal aortic aneurysm,10 coronary artery ectasia,11,12 cerebral artery aneurysm12,13 and venous system dilatation14,15 may coexist, suggesting that a systemic abnormality may explain these vascular wall destructions.16 It is therefore reasonable to assume that the observed changes in cathepsin and cystatin C expression and activity may be the common denominator that may be found in patients with multiple manifestations of dilating vascular diseases.

Regarding the inhibitory effects of cystatin C on catabolic cathepsin enzymes, it is reasonable to expect increased vascular wall destruction leading to dilatation in involved segments. Beyond the possible inverse association between the atherosclerosis and cystatin C, it is becoming more and more obvious that decreased cystatin C expression level is associated with dilating vascular disease or positive arterial remodeling. As firstly proven by animal study of Aoki et al.,3 cathepsin enzymes and cystatin C may be good targets for novel therapeutic interventions aiming in decelerating or preventing the progression of aneurysmal disease.

Disclosures

None.

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(Stroke. 2009;40:e26-e27.)
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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.537423


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Stroke. 2009;40:e26-e27; originally published online December 18, 2008;
doi: 10.1161/STROKEAHA.108.537423

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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