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Commentary

Commentary on "Inhibition of interleukin-1beta decreases aneurysm formation and progression in a novel model of thoracic aortic aneurysms"

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HIGHLIGHTS

- Aortic aneurysm model formed mainly owing to the matrix destruction by exogenous elastase rather than endogenous MMP.
- MMPs may play a positive role in remodeling of aneurysmal wall.
- MMP2 should be a key target for investigation and treatment of aortic aneurysm.

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ABSTRACT

Aortic aneurysm is a silent but life-threatening disease, whose pathogenesis remains poorly understood. Aneurysm models have been induced in small animals to study its pathogenesis, Johnston WF et al. successfully induced a novel model of thoracic aortic aneurysms (TAA) by periadventitial application of elastase in mice. We comment on this model according to our experiment. We hypothesize that endogenous MMPs, especially MMP2, play a vital role in complex repair process of aneurysmal wall, which should be a key target in the investigation and treatment of aortic aneurysms.

Aortic aneurysm, including abdominal aortic aneurysm (AAA) and thoracic aortic aneurysms (TAA) is a silent but life-threatening disease [1], whose pathogenesis remains poorly understood [2]. Aneurysm models have been induced in small animals to study its pathogenesis, of which medial injury aneurysm induced by elastase or calcium chloride is a popular model. A "classical theory" is that aneurysms develop after infusion of exogenous elastase owing to an inflammatory cascade, which causes matrix destruction and aneurysm formation by matrix metalloproteinases (MMPs). It seems that MMPs play an "evil" role in the formation of aortic aneurysm, and studies try to break this "vicious circle" by inhibiting MMPs.

Johnston WF et al. successfully induced a novel model of TAA by periadventitial application of elastase in mice, which generated large aneurysms in a shorter time frame (2 weeks) than $CaCl_2$ model (16 weeks) [3]. The authors found that IL-1β is upregulated in human TAA and suggest this contributes to the development of TAA in their model. However, samples were harvested from end-stage human TAA, so whether IL-1β plays a vital role in the initiation of TAA is uncertain. They decreased MMP9 expression by IL-1β and IL-1R knockout, which is closely related with inflammation, and targeting inflammatory aspects of TAAs may provide insight into TAA formation and treatment. The authors claimed that a model that requires months to years to evaluate treatment options is not useful for investigational purposes. We do not agree with this opinion, considering that their fast-induced model is quite different to human TAA, whose formation is multifactorial and evolves over years. Previously, we modified rabbit AAA by similar methods without satisfactory outcomes, which do not enlarge progressively and even heal spontaneously [4–6]. Although authors emphasized different mechanics and genetic origins between TAA and AAA,

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they produced TAA by the same method of AAA, and admitted that their TAA model showed almost same characteristics with AAA. It seems that this TAA model is not so revolutionary. TAA decreased in size from 2 to 4 weeks after elastase treatment. This healing period is the main limitation of fast-induced model, same phenomenon is found in rabbit AAA, which is successfully overcome in our novel enlarging model [7]. Drugs therapy for treating aortic aneurysm may be more challenging in this enlarging model than fast-induced model. Of note, our enlarging model does not involve atherosclerosis, which enlarges under hemodynamic condition induced by aortic coarctation, however, coarctation is seldom found in human AAA.

In our model, a lower concentration of elastase incubation for 30 min was unable to induce AAA formation [5], and aneurysm developed only when aortic wall was destroyed dramatically by elastase of high concentration [5]. Yamaguchi et al. [8] found that elastin fibers degenerate immediately after elastase infusion in traditional elastase-induced model, and concluded that rat AAA formation had nothing to do with endogenous MMPs produced by the infiltrating cells, but due to the exogenously infused elastase itself. These fast-induced models are controversial, although they have been widely used for investigating the pathogenesis of aortic aneurysm. We hypothesize that aortic aneurysms formed mainly because of matrix destruction by exogenous elastase rather than by endogenous MMPs, and MMPs may play a positive role in remodeling the aneurysmal wall, which cause the self-healing process of fast-induced model. Nowadays, Shen M et al. reported that MMP2 plays two opposing roles in aortic wall remodeling [9]. Their findings imply that inhibition of MMP2 may not serve as an applicable therapeutic target for aortic aneurysms [10].

Interestingly, AAA continued to enlarge although MMP9 positive staining and macrophages infiltration had almost disappeared after 2 weeks. MMP2 did not change significantly in knockout mice, and in our model, MMP2 kept moderate expression during a 5-month follow-up. Endogenous MMPs, especially MMP2, play a vital role in complex repair process of aneurysmal wall, which should be a key target in the investigation and treatment of aortic aneurysms.

Ethical approval

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Author contribution

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Bi Y, Zhong H:writing.

Han X, Xu K: study design.

Conflicts of interest

No conflicts of interest have been declared by the author.

Guarantor

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