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Overexpression of Cytotoxic T-Lymphocyte Associated Antigen-4 suppresses aortic immunoinflammatory responses and prevents angiotensin II-induced abdominal aortic aneurysm formation in mice

Authors:
H Amin¹, N Sasaki², T Yamashita³, T Mizoguchi³, T Hayashi³, T Emoto³, T Matsumoto³, N Yoshida³, T Tabata³, S Horibe², S Kawauchi², Y Rikitake², K Hirata³, ¹Faculty of Medicine Universitas Indonesia - Jakarta - Indonesia, ²Kobe Pharmaceutical University, Laboratory of Medical Pharmaceutics - Kobe - Japan, ³Kobe University, Division of Cardiovascular Medicine, Department of Internal Medicine - Kobe - Japan,

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Aims-Vascular inflammation via T-cell-mediated immune responses has been shown to be critically involved in the pathogenesis of abdominal aortic aneurysm (AAA). T-cell coinhibitory molecule cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) is known to act as a potent negative regulator of immune responses. However, the role of this molecule in the development of AAA remains completely unknown. In the present study, we determined the effects of CTLA-4 overexpression on experimental AAA.

Methods and results-We continuously infused 12-week-old CTLA-4 transgenic (CTLA-4-Tg)/apolipoprotein E–deficient (Apoe–/–) mice (n=35) or control Apoe–/– mice (n=40) fed a high-cholesterol diet with angiotensin II by implanting osmotic mini-pumps and evaluated the development of AAA. Ninety percent of angiotensin II-infused mice developed AAA, with 50% mortality because of aneurysm rupture. Overexpression of CTLA-4 significantly reduced the incidence (66%), mortality (26%), and diameter (18%) of AAA (incidence: P=0.0104; mortality: P=0.031; diameter: P=0.011). These protective effects were associated with a decreased number of effector CD4+ T cells and the downregulated expression of costimulatory molecules CD80 and CD86, ligands for CTLA-4, on CD11c+ dendritic cells in lymphoid tissues. In addition, by performing in situ zymography of the abdominal aortic aneurysm lesions, we observed a trend toward a decrease in MMP activity in the aneurysmal lesion following overexpression of CTLA-4. Finally, CTLA-4-Tg/Apoe–/– mice had reduced macrophage and CD4+ T cell accumulation and MMP activity in the aneurysmal lesion, leading to attenuated aortic inflammation, preserved vessel integrity, and decreased susceptibility to AAA and aortic rupture.

Conclusion-Our findings suggest that CTLA-4 protects against AAA by suppressing immunoinflammatory responses and could be an attractive therapeutic target for AAA.