A01-1 The role of the neutrophil-derived MMP9 in the acute aortic dissection onset

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Acute aortic dissection (AAD) is a life-threatening vascular disease which should be treated in an appropriate manner. Lifestyle diseases are the important risk factors but the mechanisms remain unknown. Matrix metalloproteinases (MMPs) are implicated in the development of chronic vascular diseases and it is reported that MMP9 inhibition results the aneurysm diameter reduction. To define further role of MMPs in AAD, we screened circulating MMPs and angiotensin II. MMP9 and angiotensin II were elevated significantly in blood samples from AAD patients than in those from the other group patients. And in immunohistochemistry with AAD patients aortas, it was suggested MMP9 was derived from neutrophils. Based on these findings we established a novel AAD model by infusing angiotensin II to immature mice that had been received a lysyl oxidase inhibitor. AAD was developed successfully with 100% incidence in 24 hours after angiotensin II administration. The incidence of the AAD was only 10% by the administration of norepinephrine instead of angiotensin I1. In this model neutrophil infiltrations were observed in the intima of the aorta and the overexpression of MMP9 was demonstrated by reverse transcription polymerase chain reaction, gelatin zymography, and immunohistochemistry. The incidence of AAD was reduced significantly by 60%, 40% following the administration of an MMPs inhibitor and anti-granulocyte-differentiation antigen-1 antibody respectively and was blocked almost completely in MMP-/⁻ mice without any influence on neutrophil infiltration. These data suggest that AAD is initiated by neutrophils that have infiltrated the aortic intima and released MMP9 in response to angiotensin II.