論　文　内　容　要　旨

Induction of *Timp1* in Smooth Muscle Cells during Development of Abdominal Aortic Aneurysms

(腹部大動脈瘤形成における、平滑筋細胞での *Timp1* 遺伝子誘導)

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ABSTRACT

Abdominal aortic aneurysm (AAA) is known to develop mainly by the increased diameter of aorta through metalloproteinases (MMPs). Although activities of MMPs are tightly regulated by the presence of tissue inhibitor of MMPs (TIMPs) and imbalances between MMPs and TIMPs may serve to fragility of arterial wall, little is known about TIMPs behavior in aneurysmal formation. Here, we utilized a murine experimental AAA model, and found that by immunohistochemical analysis, Timp1 as well as Mmp9 was accumulated in the medial layer of aorta. Up-regulation of *Mmp9* and *Timp1* mRNA levels was also revealed in aortic tissue in AAA by RT-PCR. In cultured vascular smooth muscle cells (SMCs), Tumor Necrosis Factor (TNF)-α significantly activated both *Mmp9* and *Timp1* expression, and they were blocked by Jun kinase inhibitor (SP600125) in a dose-dependent manner. Interestingly, a proteasome inhibitor (MG132), which is known as an agent for inhibition of the nuclear factor-kappa B (NF-kB), significantly inhibited the TNF-α-induced expression of *Timp1*, whereas MG132, which also works as an activator of c-Jun/AP-1 pathway, strongly increased *Mmp9*. Taken together, inflammatory cytokines, including TNF-α, may simultaneously induce MMPs and TIMPs for remodeling of the medial layer, leading to increased diameter of aorta, the aneurysm.