学位論文抄録

Roles of perivascular adipose tissue-secreted
angiopoietin-like protein 2 in vascular remodeling
（血管リモデリングにおける血管周囲脂肪組織由来アンジオポエチン様因子2の役割）

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Abstract of the Thesis

Background and Purpose: Perivascular adipose tissue (PVAT) is receiving much attention as a culprit in the development of cardiovascular disease (CVD) through secretion of various cytokines and growth factors called adipokines. Recent paper reported that angiopoietin-like protein 2 (Angptl2), a pro-inflammatory factor, was abundantly expressed in adipose tissue including PVAT and accelerated adipose tissue inflammation and subsequent systemic insulin resistance in obesity. However, it is unclear whether Angptl2 secreted by PVAT contributes to vascular remodeling. In this study, I investigated the role of PVAT-secreted Angptl2 in CVD development.

Methods and Results: The adipose tissue transplantation after endovascular injury was performed using adipose tissue of *Angptl2* knockout mice (*Angptl2*$^{-/-}$) and transgenic mice expressing Angptl2 in adipose tissue (*aP2-Angptl2*). Wild-type mice transplanted with PVAT from *Angptl2*$^{-/-}$ mice showed attenuated neointimal hyperplasia 4 weeks after endovascular wire injury compared to wild-type mice transplanted with wild-type adipose tissue. In contrast, wild-type mice transplanted with PVAT from *aP2-Angptl2* mice showed accelerated neointimal hyperplasia after endovascular wire injury compared to wild-type mice transplanted with wild-type adipose tissue, as evidenced by higher expression of PVAT pro-inflammatory cytokines, increasing vascular MMP-2 activity. The Angptl2 mRNA expression level in PVAT was significantly increased by aging, hypercholesterolemia, and endovascular injury, which are all risk factor for coronary heart disease (CHD). ANGPTL2 expression in human epicardial (pericoronary artery) adipose tissue from patients with and without CHD was unchanged in immunohisitochemical and RT-PCR analysis. Interestingly, *ANGPTL2* and *ADIPONECTIN* expression in epicardial adipose tissue of non-CHD patients indicated a positive correlation, whereas the correlation was not seen in CHD patients. However, ANGPTL2 and TNF-α expression in epicardial adipose tissue of CHD patients indicated a positive correlation, whereas the correlation was not seen in non-CHD patients. These results suggested that the balance of ANGPTL2 and TNF-α, the representative proinflammatory cytokine, or ADIPONECTIN, the representative anti-inflammatory cytokine, was broken in epicardial adipose tissue of CHD patients compared to non-CHD patients.

Conclusions: PVAT-secreted Angptl2 accelerates neointimal hyperplasia formation after endovascular injury by promoting PVAT inflammation leading to development of CVD.