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TRANSPLANTED PERIVASCULAR ADIPOSE TISSUE PROMOTES DESTABILIZATION OF ATHEROSCLEROTIC PLAQUE IN APOLIPOPROTEIN E-DEFICIENT MICE

Moderated Poster Contributions
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Background: Perivascular adipose tissue (PVAT) accelerates plaque progression and increases cardiovascular risk. We tested the hypothesis that PVAT contributes to plaque vulnerability and investigated whether endoplasmic reticulum stress (ER stress), which is the characteristic of obese adipose tissue, plays a role in the paracrine effect of PVAT.

Methods: We transplanted thoracic aortic PVAT or subcutaneous adipose tissue as a control, from donor mice to carotid arteries of recipient apoE$^{-/-}$ mice after removing common carotid artery collar placed for 6 weeks. 2 weeks after transplantation, ER stress inhibitor 4-phenyl butyric acid (4-PBA) was locally administrated to the transplanted PVAT and then animals were euthanized 4 weeks later. Immunohistochemistry was performed to quantify plaque composition and neovascularization. Mouse angiogenesis antibody array kit was used to test the angiogenic factors produced by adipose tissue.

Results: Transplanted PVAT increased the macrophage infiltration, lipid core, intimal and vasa vasorum neovascularization and MMP9 expression while decreased smooth muscle cells and collagen in atherosclerotic plaque. 4-PBA-treated PVAT improved the lesion composition and stabilized the plaque. Antibody array analysis showed that 4-PBA modulated several pro-angiogenic (MCP-1, IL-6 and GM-CSF) and anti-angiogenic factors (PF-4) secreted by PVAT. However, the supernatant of 4-PBA treated-PVAT would inhibit tube formation and migration of endothelial cells and *ex vivo* mouse aortic ring angiogenesis. mRNA expression and protein levels of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) were markedly elevated in adiopocytes under ER stress and suppressed by 4-PBA, suggesting that 4-PBA improved the plaque vulnerability in part through reduing production of GM-CSF in PVAT. In addition, ER stress enhanced NF-κB binding to the promoter region of the mouse GM-CSF gene confirmed by ChIP analyses.

Conclusions: Our findings demonstrate that PVAT promotes atherosclerotic plaque vulnerability and ER Stress inhibitor 4-PBA attenuated its paracrine effects in part through decreased GM-CSF expression in PVAT.