The Functional Implication of Novel Inflammatory Mediators on the Atherogenesis and Metabolic Derangement

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Accumulating evidence suggests that obesity provokes chronic inflammation in adipose tissue, which is associated with insulin resistance. Chronic inflammation in vasculature also plays a central role in the pathogenesis of atherosclerosis. However, the initiation of sterile inflammation in the vasculature and adipose tissue remains largely unknown. Metabolic disorders cause degeneration of cells in these organs, which increases the release of cell free DNA (cfDNA). We hypothesized that cfDNA released from degenerated cells provokes inflammation via Toll-like receptor (TLR) 9, originally known as a sensor of exogenous DNA fragments, contributing to the pathogenesis of these diseases.

Metabolic disorders induced by angiotensin II infusion to apolipoprotein E-deficient mice or high-fat feeding to wild-type mice significantly increased plasma levels of cfDNA. In both models, genetic deletion of TLR9 inhibited macrophage accumulation and inflammation in target organs, leading to attenuation of atherosclerosis or insulin resistance, respectively. Bone marrow (BM) reconstitution with wild-type BM completely restored the attenuation of insulin resistance observed in fat-fed TLR9-deficient mice. Furthermore, administration of an inhibitory oligonucleotide for TLR9 to fat-fed wild-type mice reduced inflammation in adipose tissue and insulin resistance. In vitro experiments demonstrated that macrophages stimulated with CpG-ODN, agonistic oligonucleotide for TLR9, or cfDNA extracted from degenerated endothelial cells or adipocytes markedly increased the expression of MCP-1 in wild-type macrophages but not in TLR9-deficient macrophages. Furthermore, in human subjects, plasma cfDNA level was associated with coronary atherosclerosis and insulin resistance.

These results suggest that cfDNA promotes chronic inflammation in the vasculature and adipose tissue via TLR9 and causes atherosclerosis and insulin resistance. cfDNA-TLR9 axis may play a pivotal role in the pathogenesis of atherosclerosis and insulin resistance and may serve as a novel therapeutic target.

Recently, we also reported that activated factor X (FXa), which plays a key role in the coagulation cascade, contributes to the pathophysiology of chronic inflammation in vessel wall and adipose tissues through the activation of protease-activated receptors (PARs). In this symposium, I would like to present our recent findings on the roles of novel mediators in the pathogenesis of chronic inflammation induced by lifestyle-related diseases.