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Atherosclerosis is the most important complication of type 2 diabetes and insulin resistance (IR), but its underlying mechanisms are not fully understood. Hepatic IR has been shown to produce dyslipidemia which is a significant risk factor for atherosclerosis.
Atherosclerotic plaques that are prone to rupture and cause cardiovascular disease are characterized by necrotic core formation and fibrous cap thinning. The former process, particularly prominent in the lesions of diabetics, results from lesional macrophage (Mf) apoptosis together with defective phagocytic clearance of the apoptotic Mfs. In recent years, our laboratory and others have shown that advanced lesional Mf death is characterized by activation of the endoplasmic reticulum (ER) stress pathway known as the unfolded protein response (UPR). Recently we have discovered that ER stress-induced Mf apoptosis involves a calcium-responsive kinase called calcium/calmodulin-dependent protein kinase g (CaMKIIg). In particular, CaMKIIg is activated through ER-released calcium during ER stress and serves as a link between ER stress and downstream apoptotic pathways in Mfs. To determine whether CaMKII activation in ER-stressed lesional Mfs promotes Mf apoptosis and plaque necrosis, we will breed macrophage-targeted CaMKIIg-deficient mice and subsequently measure plaque necrosis. Moreover, at the level of hepatocyte, we found that CaMKII activity is increased in the liver of both genetic and diet-induced mouse models of obesity, and Camk2g-/- mice on a high fat diet (HFD) are protected from IR. Additionally, our new data indicate that CaMKII deficiency alters the dyslipidemic profile in IR. Analysis of plasma lipids revealed that Camk2g-/- mice on HFD had significantly lower plasma triglycerides, cholesterol levels, and free fatty acids compared with WT mice on HFD. Consistent with the decrease in serum lipids, hepatic lipid accumulation was also lower in the Camk2g-/- mice on HFD. To determine whether CaMKII, through its effect on insulin sensitivity, alters the dyslipidemic profile associated with obesity, we will breed liver-specific CaMKIIg and study lipid metabolism. This overall concept presents an opportunity for novel therapeutic strategies directed against progression of atherosclerosis, namely through the elucidation of mechanisms that control in-vivo macrophage apoptosis at the arterial wall and modalities aimed at alleviating proatherogenic systemic risk factors associated with IR.