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The marked increase in cardiovascular disease (CVD) in patients with type 2 diabetes (T2D) demands an **integrated** approach to cardiometabolic disease. A major goal of the PI's lab is to elucidate common mechanisms in distinct cell types that contribute to both insulin resistance and atherosclerosis. We have shown that obesity/insulin resistance and atherosclerosis activate a CaMKII/MK2 kinase pathway in hepatocytes (HCs) and macrophages (Mϕs), respectively. In **HCs**, this pathway disrupts insulin receptor signaling, leading to systemic insulin resistance, and also down-regulates tissue plasminogen activator (tPA), which predicts higher risk of atherosclerotic CVD. In **Mϕs**, the pathway promotes plaque progression by impairing apoptotic cell clearance (efferocytosis) and inflammation resolution. We have evidence that part of the mechanism involves CaMKII-mediated suppression of LXRα. Additional data suggest that the HC pathway, by inducing hyperinsulinemia, amplifies the lesional Mϕ pathway, which predicts exacerbated plaque progression. In this context, **the overall objective is to investigate the mechanisms and consequences of the CaMKII/MK2 pathways in HCs and Mϕs in metabolism and atherosclerosis**. In Aim 1, we will investigate the role of Mϕ CaMKII in advanced atherosclerosis and its exacerbation by insulin resistance. We hypothesize that the CaMKII/MK2 pathway in Mϕs promotes advanced atherosclerosis by impairing resolution and by downregulating LXRα, which disrupts MerTK-mediated efferocytosis. To test this hypothesis, we will use WD-fed *Ldlr*$^{-/-}$mice with myeloid-CaMKII KO, with or without other alterations, *e.g.*, suppressed myeloid LXRα and MerTK. We will also feed the mice an atherogenic/diabetogenic diet to test the hypothesis that the Mϕ CaMKII pathway will be exacerbated by insulin resistance via suppression of Mϕ IR signaling (above) and that suppression of myeloid-CaMKII KO will dampen this exacerbation and its consequences. In Aim 2, we will test the hypothesis that activation of the CaMKII/MK2 pathway in HCs in obesity promotes atherosclerosis by at least two mechanisms. First, hyperinsulinemia down-regulates insulin signaling in Mϕs, elevates cytoplasmic calcium, and activates CaMKII, which is a direct link to Aim 1. Second, we have exciting new *in vivo* data that the HC pathway suppresses circulating tPA activity, and low tPA is a risk factor for atherosclerotic CVD, with relevance to T2D. We will test the hypothesis that silencing the CaMKII pathway in HCs in insulin-resistant *Ldlr*$^{-/-}$ mice will lessen advanced atherosclerosis by suppressing the Mϕ pathways outlined in Aim 1 and also by increasing tPA. Then, based on our recent publication, we will treat the mice with a specific inhibitor of the pathway to (a) intervene in a temporal manner to study the role of the pathway in atherosclerosis progression and regression; and (b) as a proof-of-concept test of the therapeutic potential of our discoveries. In summary, successful completion of this proposal will offer new mechanistic insight and potential therapeutic targets related to the integrated problem of cardiometabolic disease, which is a deadly and expanding epidemic.