Dr. Alan Tall

In Type 2 diabetes and metabolic syndrome, the liver appears to remain sensitive to the effects of insulin on lipogenesis and VLDL lipid and apoB secretion. In collaborative studies with Dr Accili, we showed that Ldlr-/- mice with genetically reduced levels of insulin receptors (IRs) in liver had decreased VLDL secretion and atherosclerosis. However, in mice with functioning LDLRs, restricted hepatic insulin signaling also led to diminished LDLR levels, indicating that the ability of insulin signaling to increase VLDL secretion is offset by an increase in LDLR levels. Recent studies have shown that the regulation of VLDL secretion and LDLR levels by insulin signaling may be mediated via effects on hepatic mTOR activity. Interestingly, mTOR signaling has been found to repress expression of Sort (a gene recently identified in GWAS of CAD and LDL levels), leading to increased VLDL triglyceride and apoB secretion. Preliminary results indicate that these effects may be mediated by mTOR-induced ER stress, leading to increased expression of ATF3, a transcriptional repressor of Sort. In contrast, the levels of LDLR appear to be regulated by a distinctive pathway downstream of mTOR that leads to decreased expression of Pcsk9 and a post-transcriptional increase in LDLR. The proposed studies will test the hypothesis that hepatic mTOR signaling acts as a central hub integrating signals from insulin and nutritional factors to regulate VLDL secretion and LDLR levels. This hypothesis will be tested using recently available mice with liver-specific knock-outs of key molecules regulating hepatic mTOR activity i.e. Li-Tsc1KO (increased mTOR1 activity) and Li-RapKO mice (reduced mTOR1 activity). With Drs Accili and Tabas, we will seek to show that genetic manipulations of insulin signaling that affect VLDL secretion and LDLR act upstream of mTOR, while ER stress, ATF3 and Sort act downstream of mTOR to regulate VLDL apoB and lipid secretion. With Dr Tabas, we will analyze liver samples from obese and lean subjects to determine if similar regulation of Sort occurs in humans. These studies should provide new insights into the regulation of VLDL secretion and LDLR levels in subjects with obesity and hyperinsulinemia.
