Dr. Henry Ginsberg

Project Summary:
Assembly and Secretion of Apo B Containing Lipoproteins: The dylipidemia of insulin resistance is very common and is associated with increased assembly and secretion of atherogenic apolipoprotein B (apoB) containing lipoproteins, particularly the triglyceride (TG)-enriched very low density lipoproteins (VLDL). Recently, hepatic steatosis, or non-alcoholic fatty liver disease (NAFLD), has emerged as an additional component of the phenotype. Pharmacologic approaches that would benefit both plasma lipid levels and hepatic fat are limited. A direct path to reducing plasma levels of atherogenic apoB-containing lipoproteins would be inhibition of apoB or TG synthesis and/or assembly into a VLDL. However, efforts to take this path have been associated with severe steatosis eg, inhibition of microsomal triglyceride transfer protein (MTP) or modest steatosis eg, inhibition of apoB synthesis using antisense oligonucleotides (ASO). Our preliminary data suggests that autophagy can play an important role in protecting the liver from steatosis while effectively reducing VLDL secretion. Thus, when we treated mice with MTP ASO, significant reductions in VLDL secretion were associated with severe steatosis. However, treatment with apoB ASO led to similar reductions in VLDL secretion but no increased steatosis. Further investigations revealed that apoB ASO treatment stimulated endoplasmic reticulum (ER) autophagy that was associated with increased fatty acid (FA) oxidation. Using this as a foundation, we will test the following hypothesis that Reduced availability of apoB in the ER, without concomitant reductions in ER TG, stimulates autophagy, which protects the liver from steatosis with the following aims: Aim 1a. To characterize the effects of inhibiting apoB synthesis, without altering TG delivery to the ER lumen, on hepatic lipid homeostasis and autophagy using mouse models. Aim 1b. To characterize the molecular basis for ER autophagy in cells with inhibited apoB synthesis. We will then extend our studies beyond the specific model of inhibition of apoB synthesis to address the more common states where hepatic lipid metabolism is perturbed: increased FA delivery to the liver, insulin resistance with increased apoB secretion, and perturbations of ER function associated with ER stress. Here we will test the hypothesis that ER autophagy is a mechanism for maintaining homeostasis in the secretory pathway whenever abnormal VLDL assembly and/or secretion lead to ER stress and the UPR with two aims: Aim 2a. To characterize, in greater detail the mechanism whereby FA-induced ER stress and the UPR stimulate autophagy. Aim 2b. To characterize the effects of overexpression of apoB on ER stress, the UPR, and autophagy. The detailed and broad-based studies of autophagy and apoB proposed herein could provide new approaches to reducing VLDL secretion while avoiding hepatic steatosis.
