Dr. Ze Zheng

2015 Russell Berrie Foundation Scholar Award

Dach1: A Hepatocyte Transcriptional Co-Repressor that Promotes Insulin Resistance in Obesity

Ze Zheng, MD, PhD

Mentor: Ira Tabas, MD, PhD

Defective insulin receptor signaling in hepatocytes represents a critical cellular process that links obesity to insulin resistance and type 2 diabetes (T2D). As described in three recent papers by the Tabas laboratory (*Cell Metabolism* 2012, 2013, *Nature* 2012), obesity activates hepatocyte CaMKII, which in turn activates an ER stress pathway that suppresses insulin signaling in hepatocytes. When any molecule in this pathway is silenced in obese mice, hepatocyte insulin signaling, glucose metabolism, and insulin sensitivity are improved. The pathway is activated in the livers of obese humans and in palmitate-treated primary human hepatocytes. Recent work in the lab has revealed the following pathway linking CaMKII to ER stress in hepatocytes in obesity: CaMKII $\Rightarrow$ p-HDAC4 $\Rightarrow$ HDAC4 nuclear exclusion $\Rightarrow \downarrow$ sumoylation of the co-repressor Dach1 $\Rightarrow \uparrow$ Dach1 $\Rightarrow \downarrow$ *Atf6* (verified by ChIP) $\Rightarrow \downarrow$ chaperone genes $\Rightarrow \uparrow$ ER stress $\Rightarrow$ insulin resistance. Hepatocyte-specific silencing of Dach1, or replacement of Dach1 with a DNA-binding mutant, markedly improves hepatocyte insulin signaling and systemic insulin sensitivity in obese mice. Moreover, analysis of human liver biopsy specimens shows a strong correlation between BMI and Dach1. Dach1 has never before been implicated in liver metabolism, and while part of effect of Dach1 is via repression of *Atf6*, our findings indicate that there are other Dach1 targets that contribute to metabolic disturbance. In this context, the overall goal of this proposal is to elucidate other key targets of Dach1 in hepatocytes that mediate pathologic metabolic pathways in obesity. Aim 1 will identify the hepatocyte genes that are repressed by Dach1 in obesity through genomic approaches to acquire an unbiased genome-wide snapshot of key transcriptional target genes repressed by Dach1 in hepatocytes in the setting of obesity. Aim 2 will determine the functional metabolic consequences of key genes that are repressed by hepatocyte Dach1 in obesity by *in vitro* and *in vivo* causation studies. In summary, backed by robust causation data on the importance of Dach1 in insulin resistance in obese mice and by human data showing that liver Dach1 increases with obesity, successful completion of my proposal will add new molecular genetics, biochemical, and physiological insight into hepatocyte-mediated mechanisms linking obesity with metabolic disturbance.