Dr. Rebecca Haeusler

Cardiovascular disease (CVD) remains the leading cause of death and disability in the country. Available therapies are inadequate, in part because they fail to redress the primary defects in many patients at high risk for CVD. The metabolic syndrome and diabetes are two major risk factors for CVD, and they are associated with a characteristic constellation of lipid metabolic abnormalities that accelerate atherogenesis, including high serum triglycerides, low high-density lipoprotein cholesterol (HDL-C), and accumulation of liver fat, defects that are poorly responsive to current hypolipidemic agents. Understanding the physiological and molecular mechanisms of these defects will expand the repertoire of targets for atherosclerosis treatment and prevention. However, a crucial gap in our knowledge exists: we do not know why triglycerides rise and HDL-C falls in the natural history of the metabolic syndrome. The liver is of critical interest, because it straddles both glucose and lipid metabolism, and it has become clear that the notion of "insulin resistance" can not explain all of the metabolic defects present in the liver. I am interested in exploring non-canonical connections among signaling pathways that drive hepatic glucose and lipid metabolism, in the hope of enlisting new players in the therapeutic approach to CVD. In preliminary data, I demonstrate a heretofore unknown link between the canonical Akt-FoxO pathway, bile acid (BA) composition, and lipid synthesis. To investigate this pathway, I propose three aims: in Aim 1, I will examine the role of the BA receptor FXR in linking FoxO-dependent transcription with lipogenesis; in Aim 2, I will investigate the requirement for the oxysterol receptor LXR and the role of cholesterol in this process; and in Aim 3, I will study the effect of FoxO-dependent BA composition on the activity of the cell surface BA receptor, TGR5, in peripheral tissues, as a potential extra-hepatic mechanism of impaired lipid metabolism. These data will provide a roadmap to design new therapeutic interventions in the treatment of dyslipidemia within the rapidly growing population of people with the metabolic syndrome.
