Acute TLR4 Activation and Improved Glucose Clearance

Toll-like receptor 4 (TLR4) is integral to an innate immune response and is the receptor for the endotoxin, lipopolysaccharide (LPS). It has been shown that activation of TLR4 with acute dosage of LPS (50pg/mL) in skeletal muscle induces a shift in substrate metabolism, favoring the oxidation of glucose as opposed to fatty acids (Frisard et al, 2010). Data from the Hulver lab shows acute treatment (2 hour) with low doses of LPS (1-20 EU) in skeletal muscle cell culture increases glucose oxidation and enhances insulin signaling, whereas chronic treatment with LPS impairs insulin signaling. Additionally, low doses (0.025 μg/kg body mass) of LPS, delivered via intraperitoneal injections, acutely (4 h post LPS injection) enhances whole-body glucose tolerance in C57Bl/6 mice. This summer, I will study the role of hepatic glucose metabolism in LPS-mediated glucose clearance. In the context of acute LPS exposure in C57Bl/6 mice treated under the same conditions stated above, liver samples will be collected and the gluconeogenesis and glycogen metabolic pathways will be studied. I will isolate RNA to perform quantitative real time PCR, and extract protein in order to conduct Western Blotting. These procedures will allow rate-limiting steps in gluconeogenesis, glycogen synthesis, and glycogenolysis to be studied at both the mRNA and protein levels. The hypotheses are that acute LPS exposure, relative to saline controls, will more potently: 1) suppress transcription and activity of proteins important for gluconeogenesis and glycogenolysis, and 2) increase transcription and activity of proteins important for glucose uptake and glycogen synthesis.