Lale Ozcan, MD

It is well established that glucagon is one of the key hormones important in glucose homeostasis, but it also plays a major role in the regulation of hepatic lipid metabolism. Although inhibition of the action of glucagon through glucagon receptor antagonists effectively lowers blood glucose in humans with type 2 diabetes, they increase plasma LDL, which has presented a significant block to their development as type 2 diabetes drugs. Consistent with a role of glucagon in cholesterol metabolism, recent studies suggested that PCSK9 and cholesterol levels can be regulated by fasting and glucagon, however, in-depth mechanistic information is lacking. In this context, I have new exciting data suggesting that hepatic glucagon signaling is a critical link between plasma PCSK9 levels and lipid metabolism. The overall plan of my proposal is to use primary hepatocytes and mouse models to further characterize and explore the mechanisms whereby liver glucagon receptor signaling contributes to PCSK9 regulation which is critical both in terms of pathophysiology and molecular cellular biology. Using both lean and obese mouse models, I will determine the mechanism(s) of how glucagon signaling down-regulates PCSK9 protein. Additionally, in collaboration with the bariatric surgery and obesity research group at Columbia, we will determine whether markers of glucagon receptor signaling activation in human liver samples correlate with the level of plasma PCSK9. If proven, the proposed studies may suggest that future therapeutic approaches combining glucagon receptor antagonists with an anti-PCSK9 antibody may be used for treating type 2 diabetes.