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The staggering rise in prevalence of obesity and its complications are likely to define the 21st century, with wide-ranging impact on health, public policy, and economics. Aside from surgical remediation, little progress has been made in preventing or ameliorating obesity with lifestyle or pharmacologic therapies. As such, novel therapeutics that target the *complications* of obesity, including insulin resistance, fatty liver and atherosclerosis, are necessary to combat this growing problem. Recent work has demonstrated that obesity does not lead to global insulin resistance, as previously speculated. Although true that in obese mice and patients, insulin is unable to inhibit the action of the transcription factor FoxO1, leading to higher hepatic glucose production and fasting hyperglycemia, even in the "insulin-resistant" state, insulin can still functionally increase rates of fatty liver, likely through its activation of sterol regulatory element-binding protein-1c (Srebp1c) and downstream targets. Nutrient excess in obesity independently regulates hepatic lipid and glucose metabolism through activation of the mTorc1 pathway, which further exacerbates fatty liver. Importantly, genetic manipulation of FoxO, or pharmacologic inhibition of mTor, reduces atherosclerosis risk in mice.

We and others have recently shown that the transcriptional effector of Notch signaling, Rbp-Jk, interacts with both FoxO1, in differentiation, and mTorc1, in cancer. These observations provided a mechanistic foundation to search for functional interaction between Notch signaling and the insulin/FoxO1 and nutrient/mTorc1 pathways in metabolism, and provoked our hypothesis that Notch signaling may be metabolically regulated, and in turn affect metabolic pathways in times of overnutrition. This hypothesis challenged accepted dogma that Notch signaling is critical for differentiation, and thereafter quiescent unless aberrantly activated in the adult animal, resulting in tumorigenesis. Our initial studies showed that hepatic Notch function varied in response to metabolic stimuli. Notch activation in liver bimodally peaks after either a prolonged fast (when FoxO1 activation is highest) and again in late refeeding (in concert with mTorc1 activation and lipogenic gene expression). Hepatic Notch signaling is increased in obese and insulin-resistant mice, suggestive of dysregulation in the pathogenic state.

To determine if ablation of Notch signaling is sufficient to protect from obesity-induced insulin resistance, we created liver-specific Rbp-Jk knockout (*L-Rbpj*) mice. As hypothesized, *L-Rbpj* mice show improved glucose tolerance as compared to control animals when fed a high-fat diet, due to reduced FoxO1 activation, and resultant lower hepatic glucose output. *L-Rbpj* mice additionally show protection from obesity-induced fatty liver due to decreased mTorc1 signaling – this particular combination of improved glucose and fatty liver, despite unchanged body weight or fatness, is unique and suggested Notch signaling as a tractable therapeutic pathway to simultaneously ameliorate multiple obesity-related conditions. Further, recent studies have demonstrated that pharmacologic Notch inhibition reduces atherosclerosis – this triumvirate of improved glucose (by inhibiting FoxO1), improved fatty liver (by inhibiting Srebp1c) and decreased atherosclerosis suggests Notch as a *bona fide* metabolic target, which our lab intends to mechanistically evaluate. In **Aim 1**, we will examine the mechanism by which inhibition of Notch action merges with FoxO and mTorc1 signaling to reduce hepatic glucose and lipid production, and ask whether this is sufficient to protect from atherosclerosis. In **Aim 2**, we intend to probe the regulation of the Notch pathway in human disease. The fundamental question is whether hepatic Notch signaling correlates with clinical measures of insulin resistance, hepatic steatosis and/or atherosclerosis. Our overall goal is to determine whether the Notch "developmental" pathway modulates metabolic adaptation in times of nutrient excess.