

Dr. Utpal Pajvani

Obesity-related metabolic diseases in their protean incarnations are likely to define health, public policy, and economics of the 21st century. Aside from surgical remediation, progress in their treatment with lifestyle or pharmacologic therapies has been disappointing. As such, we search for novel therapeutics that target the complications of obesity, including type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), or excessive hepatic fat content. Medical therapy for NAFLD is sorely lacking; the only clinical recourse is transplantation, a conundrum as available organs are always limiting. Similarly, although there are multiple therapies for diabetes available, few show durability and long-term efficacy. Persistent hyperglycemia in the face of escalating therapy is due to a failure of our currently available therapeutics, including insulin, to control the underlying pathology of type 2 diabetes, insulin resistance. We believe that we have found a novel molecular target, and a pharmacologically amenable one at that, in the Notch receptor, that has long-term potential to impact clinical care in both of these intractable obesity-related conditions.

Notch signaling has been extensively studied in the context of differentiation or cancer, but its metabolic functions are novel. Our work demonstrates that excessive Notch signaling in obesity modulates key nutrient and growth factor signaling pathways to produce the twin abnormalities of excessive hepatic glucose production (HGP) and lipid accumulation. To explain this, we hypothesize that the Notch signaling pathway, inappropriately reactivated in the obese liver, reprises its developmental role, re-associating with its molecular partners from differentiation. For instance, Notch binds to and activates FoxO1, a key regulator of HGP, leading to increased propensity for diabetes. Conversely, Notch loss-of-function protects from obesity-induced diabetes. Importantly, these effects are independent of body weight or adiposity – although just as fat, animals with less hepatic Notch signaling are healthier.

Similarly, our current work shows that Notch activates mTor, a nutrient sensor that is active in the over-fed state. Increased nutrient availability, as in obesity, leads to mTor activation and higher lipid production, even as insulin resistance is leading to high blood sugars. When Notch is inhibited using genetically engineered mice or inhibitors, again in the face of similar adiposity, mTor-dependent fatty liver is prevented. We aim now to study the molecular mechanism of this interaction, to see if we can exploit this particular combination of improved insulin signaling, and reduced mTor signaling, with Notch inhibition. Importantly, Notch signaling is therapeutically accessible, and inhibitors are in advanced clinical development for cancer. In this era of rampant obesity and limited resources for scientific discovery, our data showing that *in vivo* inhibition of Notch signaling protects from obesity-induced fatty liver and insulin resistance uncovers the possibility of alternative uses for these existing therapeutics, which our lab intends to systematically evaluate.