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To study vitamin A (retinol) mobilization specifically from hepatocyte or from adipocyte stores, we generated two lines of transgenic mice that express human retinol-binding protein 4 (hRBP4) either in hepatocytes or in adipocytes (adi-hRBP4 mice). While undertaking these studies, we found that 3-4 month old chow fed male adi-hRBP4 mice display statistically significant impairments in glucose clearance and elevated fasting hepatic triglyceride (TG) levels. There is a large human literature which proposes that adipose-derived RBP4 is casually involved in the development of insulin resistance and other component diseases collectively referred to as the metabolic syndrome. It has been hypothesized that RBP4 synthesized in adipocytes is a factor that links obesity with impaired insulin responsiveness and non-alcoholic fatty liver development. The adi-hRBP4 mice display a phenotype that is very similar to that which has been reported for obese insulin resistant humans. We propose that the adi-hRBP4 mice are an excellent model in which to investigate the molecular processes giving rise to insulin resistance and metabolic disease development. The studies we propose are
aimed at understanding the basis for the impaired glucose clearance and elevated fasting hepatic TG phenotypes of adi-hRBP4 mice. The new information obtained from the study of these mice will be directly relevant for understanding obesity induced metabolic disease in humans.

We are proposing two Specific Aims. The first will employ chow and high fat fed adi-hRBP4 mice and matched littermate controls to assess the involvement of factors, like retinol binding to RBP4 and interactions of RBP4 with its cell surface receptor STRA6, that are canonically associated with RBP4, facilitating vitamin A delivery to tissues. The second Specific Aim, again employing chow and high fat fed adi-hRBP4 and matched control mice, will explore pathways that are non-canonical ones for understanding RBP4 actions. We hypothesize that elevated adipocyte synthesis of RBP4, as would occur in obesity, will affect immune cell infiltration into adipose tissue bringing about an altered tissue inflammatory response. The proinflammatory factors then generated in adipose tissue adversely influence metabolism in other tissues giving rise to disease, such as fatty liver development. As part of this Specific Aim, we will also systematically explore possible metabolic differences in fatty acid and TG metabolism in the livers of adi-hRBP4 mice that may account for the elevated fasting TG levels we have observed. Collectively, our studies will extend understanding of RBP4 actions in the body and of how RBP4 is involved in metabolic disease development.