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Vitamin A is required by the body for maintaining many important physiological functions including normal growth and development, a healthy immune response, normal reproduction, and normal vision. Owing to the importance of vitamin A in so many essential physiological processes, the body has developed an ability to store vitamin A, primarily in liver but also in adipose tissue. At present, relatively few details are known about the molecular processes responsible for vitamin A storage and metabolism in hepatocytes and hepatic stellate cells (HSCs), the two liver cell types involved in vitamin A storage and metabolism. Similarly, relatively little is known about the molecular processes that are important for mediating vitamin A storage and metabolism in adipocytes, the cell type in adipose tissue responsible for vitamin A accumulation. The investigations proposed in this application are aimed at providing new and more detailed understanding of these processes.

The overall goal of the project is to establish how RBP mobilizes retinol from HSC and adipocyte stores. The studies being proposed will be carried out in mice that express retinol-binding protein (RBP) in a cell type-specific manner. Specific Aim 1 explores the roles that RBP synthesized specifically in hepatocytes, specifically in HSCs or in both cell types have in the mobilization of HSC vitamin A stores into the circulation. This has been a matter of considerable controversy for over 20 years. An underlying goal of Specific Aim 1 is to resolve this controversy. As part of Specific Aim 1 we will develop a mathematical (compartmental) model describing the flux of retinol amongst hepatocytes, HSCs, the circulation, and peripherial tissues and how this is influenced by expression of RBP in hepatocytes and/or HSCs. Adipocytes are also a significant site of vitamin A storage in the body and also an important site of RBP synthesis. Importantly, it has been proposed that RBP synthesized by adipocytes acts to lessen whole body insulin responsiveness. Little is known the role of RBP in facilitating vitamin A mobilization from adipocytes or how this might relate to insulin signaling. Specific Aim 2 will define the role of RBP in facilitating vitamin A mobilization from adipocytes, establish whether adipocyte secretion of RBP is dependent on retinol availability, and delineate how this may be linked to role of adipose-derived RBP in signaling peripheral tissues to become less insulin responsive, giving rise to type II diabetes.