USING A MOUSE MODEL TO STUDY THE ROLE OF IMMUNE SYSTEM IN TYPE II DIABETES: DELETION OF RETINOL TRANSPORTER IN DENDRITIC CELLS PROTECTS MICE FROM OBESITY INDUCED GLUCOSE INTOLERANCE AND INSULIN RESISTANCE

Lilly Kanishka (Tetyana Forostyan, Sihem Boudina PhD)
Department of Oncological Sciences,
Department of Nutrition and Integrative Physiology,
Division of Endocrinology and Program in Molecular Medicine

Background
An epidemic of diet induced metabolic diseases, such as Type 2 Diabetes, is affecting human population worldwide, and has been recognized as a major health problem in modern society. Insulin resistance, the hallmark of diabetes, is driven by inflammation of the adipose tissue triggered by CD11c+ dendritic cells. Although obesity triggered immune response has been linked to insulin resistance, the underlying mechanisms have not been established. Up-regulation of retinol binding protein 4 has been shown to drive inflammation in fat and precede development of insulin resistance in humans and mice. This study was aimed to generate a mouse strain with a deletion of retinol binding protein 4 receptor STRA6L in CD11c+ immune cells, in order to study the role of retinol transport and signaling in development of diet induced obesity and insulin resistance.

Methods
Mice with loxP insertion in STRA6L gene were bred with mice expressing Cre under CD11c promoter. The STRA6L flx/+ , CD11c-Cre offspring males were bred again with STRA6L flx/flx females maintained on a diet containing 4 u/kg of Vitamin A, to generate homozygous KO (STRA6L flx/flx, CD11c-Cre) and littermate control WT (STRA6L flx/flx) animals. Male mice were placed on a high fat diet at 10 weeks old. Body lean versus fat composition was determined using Nuclear Magnetic Resonance spectrometry. Glucose Tolerance Tests (GTTs) and Insulin Tolerance Tests (ITTs) were done using i.p. injections. Body weight, composition, and insulin sensitivity were assessed before and during high fat diet study. At the end of the study, the tissues were collected and frozen for protein and RNA analysis, and fixed in 4% PFA for histology.

Results
Both wild type and STRA6L KO mice gained fat mass in response to high fat diet. KO animals on a high fat diet had better performance scores on GTT and ITT tests compared to WT siblings. Histological study of epididymal fat showed reduced adipocyte hypertrophy and preserved cellularity in KO animals on a high fat diet.

Conclusions
Deletion of retinol binding protein 4 receptor STRA6L in CD11c+ dendritic cells protects mice from developing insulin resistance in response to diet-induced obesity. Our results suggest that deletion of retinol transporter in CD11c+ immune cells affects how these cells regulate metabolic homeostasis in fat.