INFLAMMATORY AND ANTI-INFLAMMATORY PATHWAYS IN INSULIN RESISTANCE INDUCTION IN OBESITY

Hannah Kanety

Institute of Endocrinology, Sheba Medical Center, Israel

The marked increase in obesity during the last decades and its strong association with insulin resistance and type 2 diabetes, have elicited interest in the underlying mechanisms of obesity-induced insulin resistance. Obesity is currently viewed as a low-grade, chronic inflammatory state, termed metaflammation, orchestrated by metabolic cells in response to excess nutrients and energy. It is associated with higher secretion of proinflammatory cytokines like tumor necrosis factor α (TNF) from adipose tissue, and with reduced secretion of the anti-inflammatory, anti-diabetic hormone adiponectin. The balance between the various cytokines and adipokines, secreted from adipose tissue, plays an important role in modulating insulin action.

We have previously shown that TNF induces insulin resistance by promoting serine phosphorylation of insulin receptor substrate (IRS)-1, and thereby compromises insulin signal propagation. We have now identified p38MAPK as an important mediator of hepatic insulin resistance both *in vivo* in animal models of obesity and *in vitro* in liver cells exposed to TNF. Whereas stress kinases like JNK phosphorylate IRS-1 directly, p38MAPK activation by TNF and additional stress stimuli, initiates ErbB receptors signaling and activation of a PI3K signaling cascade, culminating in serine phosphorylation of IRS-1 and impaired cellular response to insulin. The relevance of this novel mechanism has been confirmed also in muscle cells. Furthermore, we found that AMPK activation in muscle cells by adiponectin or by AICAR, an AMP analog, attenuates IRS-1 serine phosphorylation under stress conditions. Adiponectin receptor-1 (AdipoR1) expression in skeletal muscle plays an important role in insulin resistance and diabetes. Recent work in our lab indicates that AdipoR1 expression in human skeletal muscle is subjected to posttranscriptional regulation, including alternative splicing and translational control. These mechanisms play an important role during myogenesis and are important for whole-body insulin sensitivity.

Collectively, our studies provide new insights into the mechanisms underlying the development of insulin resistance in obesity.

ADIPOSE TISSUE FOAM CELLS IN OBESITY: ROLES IN TISSUE REMODELING AND INSULIN RESISTANCE

Hagit Shapiro[1,2], Chandrashekaran Gurunathan[1], Jong H. Lee[1], Souphatta Sasorith[1], Prerna Bhargava[1], Ruthy Shako-Levi[2], Assaf Rudich[2], Jongsoon Lee[1] and Steven E Shoelson[1]

[1]Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA and [2]Ben-Gurion University Beer-Sheva, Israel

Adipose tissue macrophages (ATMs) have been suggested to participate in the pathogenesis of insulin resistance and type 2 diabetes. In AT of obese but not lean mice and humans we have identified lipid-laden macrophages (foam cells) in crown-like structures of macrophages surrounding the adipocytes. We have developed a novel flow cytometric method for purifying AT foam cells and compared their genomic profiles to non-foam ATMs from lean mice. Results were confirmed by real-time PCR, immunohistochemistry and western blotting. The foam cells showed enhanced expression of lipid uptake/metabolism proteins such as Lpl, Fabp4, Fabp5, Fabp7, Ldlrap. Also upregulated in foam cells were extracellular matrix (ECM) proteins, including collagens (Col1, Col3, Col4, Col6), integrins (ItgaV, Itga6) and ECM modifying factors such as MMPs (MMP3, MMP12, MMP14) and cathepsins (CtsK, CtsL). AT foam cells were not clearly conformed to M1 or M2 polarities, as their corresponding mRNA levels were mixed. We have tested the functional significance of AT foam cells by selectively disrupting highly up-regulated genes in vivo; as an example Lpl (30 fold increase in foam cells) was deleted in macrophages using the *LysM-Cre* Loxp technology. HFD $lpl^{\Delta mye}$ mice showed reduced expression of Lpl not only in ATMs but also in whole epididymal adipose tissue (but not other tissues). These mice showed significant reduction in total cholesterol (22% reduction) and LDL (41%) without change in FFA, TG and FFA levels in both fasting and fed state. Both mice showed similar weight gain but HFD $lpl^{\Delta mye}$ had a significant decrease in glucose tolerance test (33% reduction), insulin (29%) and HOMA-IR (32%). At the adipose tissues levels HFD $lpl^{\Delta mye}$ showed robust fibrosis and abnormal foam cells formation. Taken together, this study identified foam cells in adipose tissue in response to adiposity in both mice and humans. The results of the genomic analysis of the foam cells and the $lpl^{\Delta mye}$ mice suggest that AT foam cells function in lipid uptake, AT remodeling and may contribute to the pathogenesis of insulin resistance and hypercholesterolemia.

HYPOTHALAMIC NEURONAL TOLL-LIKE RECEPTOR 2 PROTECTS AGAINST OBESITY

Ravid Shechter*, Anat London*, Yael Kuperman*, Ayal Ronen*, Asya Rolls, Alon Chen# and **Michal Schwartz**#
*and # = equal contributions

Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) that plays a fundamental role in the activation of the immune response against invading pathogens, as well as under sterile pathological conditions. As such, these receptors were also found to be involved in the development of obesity. This linkage was previously attributed to the destructive peripheral inflammatory processes that are often associated with obesity. Here, we introduce a novel non-immunological role of TLR2, known to recognize lipid components, as a central negative regulator of food intake in the hypothalamus. We discovered that TLR2 deficient mice (TLR2D) developed mature-onset obesity and showed decreased glucose tolerance and insulin sensitivity compared with their WT controls. Using chimeras in which the immune system of the host mice was replaced at adulthood with wild-type cells, we demonstrated that TLR2 has a non immunological role in preventing age-related obesity. The increased appetite of the TLR2D mice was associated with reduced levels of the hypothalamic anorectic peptide, α-MSH, within their arcuate nucleus, suggesting a role for this receptor in the central regulation of obesity. We further found that TLR2 expression was induced by metabolic POMC+ neurons in the hypothalamus of middle aged mice. *In vitro* cultures of a hypothalamic neuronal cell line with the well known pharmacological activators of TLR2 further substantiated the direct role of this receptor in regulating metabolic signals within hypothalamic neurons, possibly by modifying the levels of key adipokines. In summary, our study attributes a novel protective physiological role to TLR2 in the regulation of body weight and food intake, which extends beyond its defined pathological inflammatory-related functions.