BBB Seminar (BMED380)

SCAN ME

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Regulation of adipocyte hypertrophy and its impact on systemic metabolism

Siegfried Ussar
Helmholtz Munich, Germany

At times of energy surplus, most excessive energy is stored in white adipocytes in form of triglycerides. This makes white adipose tissue the primary site of energy storage. Increased lipid storage can be either facilitated by hyperplasia, the storage of fat in de novo differentiated adipocytes, or hypertrophy, the storage of fat in already existing adipocytes. Hypertrophic adipose expansion can exceed the lipid storage capacity of adipocytes, resulting in adipocyte death, inflammation and spillover of lipids to other organs such as the liver and skeletal muscle. Local and systemic inflammation in combination with ectopic lipid accumulation can then initiate the development of insulin resistance and the metabolic syndrome. Thus, understanding the mechanisms of adipocyte lipid accumulation and hypertrophy is important to develop novel therapeutic approaches dissociating obesity from the metabolic syndrome. In this context, we identified the small cell surface protein Nrac as a regulator of CD36 mediated fatty acid uptake. Loss of Nrac accelerates adipocyte fatty acid uptake leading to adipose hypertrophy. Importantly, loss of Nrac at the cell surface occurs naturally in response to increased extracellular fatty acid concentrations. Thus, we identified a novel regulatory mechanism limiting adipocyte fatty acid uptake at times of low circulating fatty acid concentrations. This allows utilization of fatty acids in organs such as the heart, requiring fatty acids for energy production. Conversely, to prevent lipotoxicity, when circulating fatty acid levels are high, loss of cell surface localization of Nrac results in elevated fatty acid influx of adipocytes for storge.

Moreover, we show that increased basal insulin secretion from pancreatic beta cells, not reaching the threshold to induce tissue glucose uptake, suppresses adipocyte lipolysis resulting in adipocyte hypertrophy in chow diet fed animals. Surprisingly, these lean chow diet fed mice showed improved glucose tolerance compared to control animals. However, feeding a hypercaloric high fat diet to mice with already enlarged adipocytes accelerated the development of insulin resistance and glucose intolerance. Thus, natural variations in basal insulin secretion could have profound effect on the predisposition for the development of metabolic disease in context of a hypercaloric diet. Overall, we reveal important mechanisms of both lipid uptake and lipolysis in the regulation of adipocyte hypertrophy.

Chairperson: Johan Fernø, Haukeland University Hospital