An adipocentric view of the development of insulin resistance
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Introduction

Summary

From the classical point of view adipose tissue is known for energy storage in the form of triglycerides. However, during the last 15 years adipose tissue gained a lot of interest due to its endocrine activity. Nowadays, adipose tissue is commonly accepted as an endocrine organ secreting numerous hormonal factors called adipokines. These adipokines are involved in divergent biological processes such as inflammation (IL-6, TNFα, IL-1β), energy metabolism (adiponectin, leptin), reproduction (leptin) and many others. In obesity and associated with it low grade systemic inflammation, the adipokine secretory profile changes, which might result in deregulation of the metabolism of the adipose tissue itself and eventually lead to systemic insulin resistance. However, the exact role of the adipose tissue in the development of insulin resistance during these conditions is not completely known, therefore in this dissertation our aims were: (1) to study the role of adipose tissue in the development of systemic insulin resistance in relation to (A) nutritional overstimulation (GIP signaling), (B) clinical parameters involved in obesity and inflammation, (C) exogenous inflammatory triggers and (2) to identify biomarkers specific for inflammation/insulin resistance in adipose tissue by means of omics technologies such as various proteomics techniques and DNA microarrays.

Glucose dependent insulinotropic polypeptide (GIP) was proposed as a link between overnutrition and insulin resistance (IR), due to the fact that in several in vitro studies it was shown to stimulate TG accumulation in the adipose tissue thereby promoting development of obesity and insulin resistance. Additionally, it was shown that GIP receptor knockout mice were protected from obesity on high fat diet. Therefore, in order to test the hypothesis that access of GIP might accelerate development of obesity/IR, we performed experiments where mice were injected with a GIP analogue during high fat or chow diets and monitored several serum biochemical parameters and expression of subsets of proinflammatory and energy metabolism genes in adipose tissue. Additionally, in order to identify GIP target genes in the adipose tissue we performed DNA-microarray to screen for adipose tissue GIP target genes. Results obtained from these studies did not confirm that excess of GIP leads directly to the accelerated development of obesity or IR, thereby excluding GIP as a direct link between overnutrition and IR in vivo. However, we identified several new GIP target genes in adipose tissue: Apo –gene family members and other genes involved in lipid metabolism, and genes with as yet unknown functions in the adipose tissue.
In order to answer the question if inflammation in adipose tissue is a cause or consequence of insulin resistance in humans, we studied gene expression of selected proinflammatory and metabolic genes in adipose tissue in non diabetic women and their relation to several clinical parameters indicative for early IR.

In our study group we found that the tested metabolic genes had altered expression associated with parameters of obesity and insulin resistance. However, we did not find such correlations for a subset of proinflammatory genes. These findings suggest that metabolic alternations in adipose tissue precede the inflammation, thereby excluding inflammation as the pivotal event leading to IR, at least in this particular patient group. Recent literature data [58] indicate that dysfunction of mitochondria and the resulting overproduction of ROS could be the key events initiating insulin resistance.

Despite the fact that there are several candidate biomarkers for systemic insulin resistance their application in clinical practice as a supporting tool for early detection and its organ specific origin is still futuristic. In this dissertation we aimed to validate if resistin is indeed a good candidate biomarker (over)produced by the adipose tissue during inflammation/insulin resistance. Our ex vivo studies did not confirm that resistin is induced by inflammation (evoked by LPS), thereby excluding it as a biomarker indicative for inflammation / insulin resistance. Moreover, we found that the human liver is an abundant source of resistin on both gene and protein levels, thereby opening new avenues for the investigations devoted to the role of resistin in the liver metabolism and its possible link to IR.

In order to find novel biomarkers and pathways indicative for inflammation/IR in adipose tissue we studied in detail the changes in the adipose tissue secretome during inflammation and compared the inflammatory adipose tissue secretome with the inflammatory liver secretome. Our study led to the identification of differential pathways and biomarkers, revealed by transcriptomic and proteomic approaches. The presence of these differential biomarkers and pathways suggests tissue specific changes in response to inflammation/insulin resistance, which could be applied for tissue specific detection and treatment of IR. The adipose tissue specific biomarkers were represented by fractalkine, tumor necrosis factor, pentraxin-related protein or interstitial collagenase (matrix metallopeptidase 1) and the liver tissue specific biomarkers were for example chemokine (C-X-C motif) ligand 9, chemokine (C-X-C motif) ligand 3, or follistatin-like 3 (secreted glycoprotein).

In conclusion, in a search for the major players in insulin resistance we found that: (excess) of GIP does not serve as a link between obesity and insulin resistance. Seeking for the
primary changes in adipose tissue gene expression in the early stages of the development of insulin resistance we found, that metabolic genes had altered expression in patients with increased HOMA and decreased HDL serum levels while the proinflammatory genes were unaffected in these patients. These findings suggest therefore, that metabolic alternations might precede inflammatory ones in the early development of insulin resistance, and exclude inflammation as a cause of IR in humans, but accommodate it as a consequence of IR.

Our finding that during inflammation adipose tissue displays a unique pattern of gene/protein expression compared to the liver, suggests that the adipose tissue specific proteins could be used as biomarkers to detect (adipose) tissue specific IR. Further investigations and validation studies should explore the possibilities for the development of novel tissue specific diagnosis of IR and thereby more targeted strategies for its treatment.