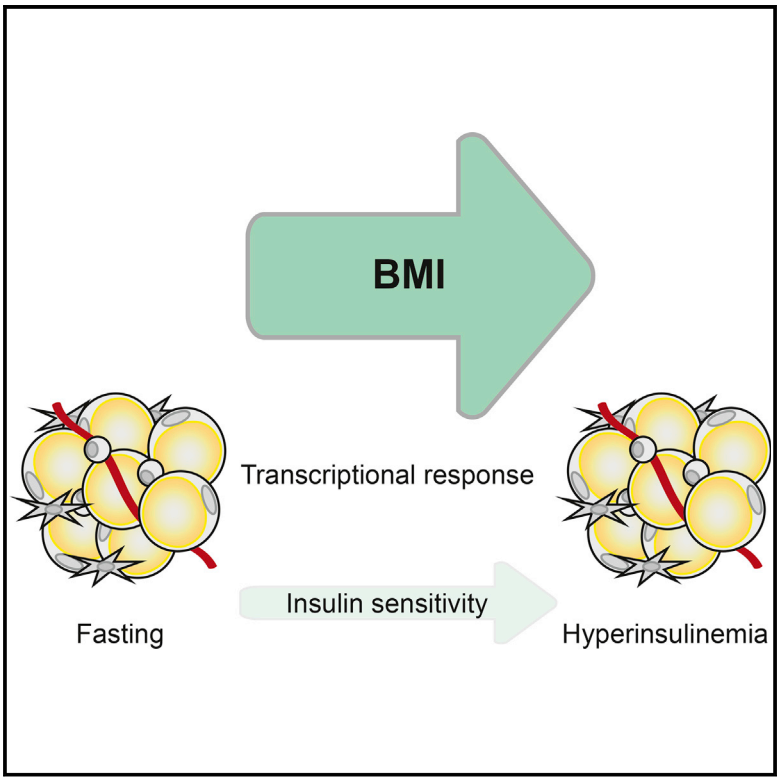
Cell Reports

The Adipose Transcriptional Response to Insulin Is Determined by Obesity, Not Insulin Sensitivity

Graphical Abstract



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In Brief

Rydén et al. performed transcriptomic profiling in adipose tissue from non-obese and obese subjects discordant in insulin sensitivity. The transcriptional response to hyperinsulinemia was similar among obese subjects and differed from that in non-obese subjects. The two obese groups differed only in a limited set of genes, thereby challenging the notion of healthy obesity.

Highlights

- Adipose gene expression is determined in non-obese and obese subjects
- Acute hyperinsulinemia induces a significant overall transcriptional response
- The transcriptional response in obese subjects differs from that in non-obese subjects
- The transcriptional response in obese subjects does not depend on insulin sensitivity

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Report

The Adipose Transcriptional Response to Insulin Is Determined by Obesity, Not Insulin Sensitivity

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SUMMARY

Metabolically healthy obese subjects display preserved insulin sensitivity and a beneficial white adipose tissue gene expression pattern. However, this observation stems from fasting studies when insulin levels are low. We investigated adipose gene expression by 5′Cap-mRNA sequencing in 17 healthy non-obese (NO), 21 insulin-sensitive severely obese (ISO), and 30 insulin-resistant severely obese (IRO) subjects, before and 2 hr into a hyperinsulinemic euglycemic clamp. ISO and IRO subjects displayed a clear but globally similar transcriptional response to insulin, which differed from the small effects observed in NO subjects. In the obese, 231 genes were altered; 71 were enriched in ISO subjects (e.g., phosphorylation processes), and 52 were enriched in IRO subjects (e.g., cellular stimuli). Common cardio-metabolic risk factors and gender do not influence these findings. This study demonstrates that differences in the acute transcriptional response to insulin are primarily driven by obesity per se, challenging the notion of healthy obese adipose tissue, at least in severe obesity.

INTRODUCTION

Up to 30% of obese subjects display normal fasting plasma glucose/lipid levels and normotension, a phenotype referred to as "metabolically healthy obesity," which implies that a significant proportion of obese individuals may need less vigorous interventions to avoid metabolic/cardiovascular complications (Blüher, 2010; Karelis, 2008; Primeau et al., 2011; Samocha-Bonet et al., 2012; Sims, 2001). A hallmark characteristic among these individuals is high insulin sensitivity. Several studies have shown that insulin-sensitive obese (ISO) subjects have lower visceral fat accumulation, less ectopic fat and arterial atherosclerosis, higher plasma adiponectin levels, and a more favorable inflammation profile than insulin-resistant obese (IRO) individuals (Blüher, 2010; Karelis, 2008; Primeau et al., 2011; Samocha-Bonet et al., 2012; Xu et al., 2013). It is also well established that the two obesity phenotypes differ in the subcutaneous white adipose tissue (sWAT) itself (Xu et al., 2013). ISO individuals have smaller fat cells and less pronounced inflammation than IRO individuals, which is also reflected at the gene expression level (Elbein et al., 2011; Qatanani et al., 2013). However, the transcriptional profiles of sWAT have been investigated in the fasting state, when insulin levels are low (Elbein et al., 2011; Qatanani et al., 2013). As insulin is expected to induce profound alterations in gene expression, it is not clear how such changes relate to insulin sensitivity and clinical profiles. This has prompted some investigators to determine the transcriptional response to insulin in sWAT collected before and during hyperinsulinemic euglycemic clamp for 6 hr. Comparisons in limited numbers of lean ISO and IRO subjects have reported some between-group differences (Soronen et al., 2012; Westerbacka et al., 2006). Although relevant, these studies were not designed to address the transcriptional response to insulin in subjects matched for BMI. Thus, in order to fully evaluate the idea of a healthy obese state, insulin responses need to be determined in obese subjects discordant in insulin sensitivity and ideally compared with those in healthy non-obese (NO) subjects.

Although ISO and IRO individuals display different clinical phenotypes, it has been a matter of debate whether they also confer different risks for cardiovascular morbidity and/or mortality (Flint et al., 2010; Lu et al., 2014; Ortega et al., 2013; Song et al., 2007). In fact, several recent meta-analyses have refuted the notion that "healthy obesity"or preserved insulin sensitivity protects against cardiometabolic complications (Fan et al., 2013; Kramer et al., 2013; Roberson et al., 2014). These controversies prompted us