Increased Inflammasome and Caspase-1 Activation in Visceral adipose tissue from Metabolically Unhealthy Obese compared to Metabolically Healthy Obese subjects

The pro-inflammatory cytokine interleukin-1 beta (IL-1β) is involved in the pathogenesis of obesity-related insulin resistance. High level of this cytokine in obese subjects results from the activation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome. Obesity is a heterogeneous disease; some patients are obese but metabolically healthy (MHO) whereas others develop metabolic disorders (metabolically unhealthy or MUO). Adipose tissue is also heterogeneous; its visceral (VAT) component is more associated with metabolic disorders than its subcutaneous (SAT) component. The aim of this study is to assess if differences in NLRP3 inflammasome activity and adipose cell composition play a role in such phenotypic and biochemical heterogeneities.

The MHO phenotype was defined as the absence of metabolic syndrome. Paired SAT and VAT adipose tissue samples were obtained from a total of 23 MUO subjects, 21 age- and BMI-matched MHO subjects and 9 age-matched lean subjects.

Relevant and significant differences were found among the three phenotypes but only in the VAT, including higher expression of IL-1β and NLRP3 mRNA, an increased secretion of IL-1β, higher levels of adipose tissue macrophages (ATMs) and granulocytes, and lower percentages of T regulatory cells in the VAT of MUO compared to MHO and lean subjects. Moreover, the caspase-1 activity and IL-1β release were higher in the ATMs from VAT of MUO compared with MHO. Similar significant differences were showed between the SAT and VAT of MUO subjects. CD11c+CD206+ ATMs, with their well-known pro-inflammatory M1 phenotype, had a higher caspase-1 activity compared to CD11c-CD206+ ATMs.

In conclusion, metabolic abnormalities are associated with an activation of the inflammasome in the ATMs infiltrating the VAT. MHO subjects have a more favorable VAT inflammatory profile.

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