REVIEW ARTICLES

Adipose tissue changes in obesity and the impact on metabolic function

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Obesity is associated with adverse alterations in adipose tissue that predispose to metabolic dysregulation. These adverse alterations include accumulation of inflammatory macrophages leading to the activation of inflammation pathways, reduction in lipid turnover, and deposition of fat in ectopic locations. These alterations are precursors to the development of insulin resistance and metabolic dysfunction. (Translational Research 2014;164:284–292)

Abbreviations: ATGL = adipose triglycerol lipase; ATM = adipose tissue macrophage; CLS = crown-like structure; CRP = C-reactive protein; CT = computed tomography; DM2 = type 2 diabetes; FFA = free fatty acid; HSL = hormone-sensitive lipase; IL-6 = interleukin-6; MCP-1 = monocyte chemoattractant protein 1; TNF-α = tumor necrosis factor alpha

INTRODUCTION

In this review, we provide an overview of adverse alterations in adipose tissue that occur with obesity and result in metabolic dysfunction. These include activation of inflammatory pathways, alterations in adipose tissue lipid metabolism, and adipose tissue distribution resulting in unfavorable adipokine profile. The focus will be on the more recent advances in the field that are at the forefront of investigation.

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INFLAMMATION AND ADIPOSE TISSUE MACROPHAGE INFILTRATION IN OBESITY

Activation of inflammatory pathways in adipose tissue is a major mechanism that contributes to the development of insulin resistance, type 2 diabetes (DM2), and metabolic disorders in obesity.[1-5] In addition to adipocytes, adipose tissue contains other cell types among which are vascular endothelial and immune cells such as adipose tissue macrophages (ATMs). Obesity is associated with increased accumulation of ATMs that secrete inflammatory cytokines, such as, tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and monocyte chemoattractant protein (MCP-1),[6,7] factors that are known to interfere with tyrosine phosphorylation of the insulin receptor and insulin receptor substrates. Reduced tyrosine phosphorylation leads to the impairment of early events in the insulin transduction pathway and development of insulin resistance.[8]

Studies in animals demonstrate that adipose tissue expansion is accompanied by macrophage infiltration,[6,7,9] switch in macrophage activation to a more proinflammatory state,[10] and high expression of inflammatory cytokines.[6,7,11-13] In humans, obesity is also associated with adipose tissue inflammation.[14] Weight

loss by diet and exercise or by bariatric surgery is associated with a reduction in ATM infiltration, adipose tissue inflammation, and improvements in insulin sensitivity in humans.[11,15] The hallmark of ATM infiltration is the formation of crown-like structures (CLSs) that assemble as ATMs aggregate around dead adipocytes to ingest the dying cells.[16] Studies in humans have shown an increase in CLS density with obesity and strong correlation between this feature and inflammation and insulin resistance.[12,17] Furthermore, CLS density is significantly related to insulin resistance in obese humans independent of body mass index (BMI) such that obese insulin resistant subjects have significantly higher CLS density compared with similarly obese but insulin-sensitive subjects.[18] CLS density is also increased in nonobese subjects with insulin resistance such as women with polycystic ovary syndrome compared with nonobese control women.[19] However, in a study of healthy nonobese humans who were given high-fat diet to induce insulin resistance, there was not an increase in ATM infiltration or adipose tissue inflammation, suggesting that adipose tissue inflammation may be secondary to obesity or insulin resistance.[20]

ATMs display varied inflammatory behavior and those that accumulate in adipose tissue with obesity are proinflammatory and display higher expression of inflammatory cytokines (eg, TNF-α) and other markers in the inflammatory pathway.[10,12,21] In contrast, macrophages residing in adipose tissue of nonobese humans or animals are anti-inflammatory in nature.[10,12] In rodents, 2 separate polarization states, M1 and M2, have been identified.[10] MI or "classically activated" macrophages have enhanced proinflammatory cytokine production (TNF-α, IL-6). M2 or "alternatively activated" macrophages have low proinflammatory cytokine production and high anti-inflammatory cytokine production such as IL-10.[10] Diet-induced obesity in rodents shifts the ATM polarization state from M2 to M1 with increased expression of genes coding for TNF-α and inducible nitric oxide synthase and decreased expression of anti-inflammatory genes such as IL-10.[10] In humans the existence of M1 and M2 macrophage polarization states has not been as well defined as in rodents.[22,23] Regardless of polarization state, the proinflammatory ATMs in obese humans and animals express the surface marker CD11c.[12,13,21,24,25] In obese humans, CD11c macrophages localize to CLS and are strongly associated with insulin resistance.[12] Increased adipose tissue expression of CD11c macrophages has also been reported in association with insulin resistance in the absence of obesity.[19,26] Ablation of CD11c macrophages normalizes insulin sensitivity in obese insulin–resistant mice[24] suggesting that these macrophages mediate the inflammatory response.

Factors that promote ATM infiltration in obesity have not been clearly identified but include adipose tissue hypoxia and hypoxia-induced fibrosis ensuing in adipocyte death.[4] Hypertrophied adipocytes in expanding adipose tissue demonstrate decreased capillary density[27-29] and reduced tissue perfusion. Reduced adipose tissue perfusion has been demonstrated with obesity in humans[27] and animals[29,30] and predisposes to lower tissue oxygenation and hypoxia. Hypoxia in turn promotes ATM infiltration,[27,30] and lowers adiponectin expression[29-31] and insulin resistance.[27] These negative consequences are mediated by hypoxia-inducible factor 1α[32,33] that has higher expression in obese states.[29,30,32] Selective inhibition of hypoxia-inducible factor 1α ameliorates adipose tissue dysfunction in high-fat diet–induced obesity in mice.[33] Additional negative consequences of hypoxia include endoplasmic reticulum[34] and oxidative stress[35] that can further predispose to adipose tissue inflammation. Other proposed mechanisms for ATM infiltration in obesity include stimulation by chemokines such as MCP-1 whose expression increases in obesity and through increased free fatty acid (FFA) flux.[4]

CIRCULATING ADIPOKINES IN OBESITY

The link between inflammation and metabolic abnormalities in obesity was first established in a report on rodents in 1993 that demonstrated induction of TNF-α expression in adipose tissue after diet-induced obesity.[36] The increase in adipose tissue TNF-α expression was associated with higher local and systemic levels of this cytokine.[36] Furthermore, neutralization of TNF-α was accompanied by a significant increase in insulin-mediated glucose uptake consistent with an improvement in insulin sensitivity in obese rodents.[36] Another report from the same year demonstrated that TNF-α impaired early events in the insulin transduction pathway by reducing tyrosine phosphorylation of the insulin receptor and insulin receptor substrates.[8] In humans, trials of TNF-α inhibition have not led to a consistent improvement in insulin sensitivity.[37-39] However, infusion of TNF-α to healthy humans has been shown to induce skeletal muscle insulin resistance.[40] Furthermore, obese humans have higher levels of C-reactive protein (CRP), which is an independent risk factor for metabolic and cardiovascular disease[41-46] and maybe directly involved in atherogenesis at the vessel wall.[47] CRP levels are also higher in obese insulin-resistant subjects compared with obese insulin-sensitive subjects.[48] Obese humans have higher expression of adipose tissue IL-6, which stimulates hepatic CRP generation.[49] Additionally, ATMs are the source of circulating prothrombotic