Is interleukin-1β a culprit in macrophage-adipocyte crosstalk in obesity?

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Adipose tissue remodeling occurs in obesity, characterized by adipocyte hypertrophy and increased infiltration of macrophages which also shift to a proinflammatory phenotype. Factors derived from these macrophages significantly alter adipocyte function, such as repressing adipogenesis, inducing inflammatory response and desensitizing insulin action. As macrophages produce a cocktail of inflammatory signals, identifying the key factors that mediate the detrimental effects may offer effective therapeutic targets. IL-1β, a major cytokine produced largely by macrophages, is implicated in the development of obesity-associated insulin resistance. In this article, we discuss recent advances in our understanding of the role of IL-1β in macrophage-adipocyte crosstalk in obesity. IL-1β impairs insulin sensitivity in adipose tissue by inhibition of insulin signal transduction. Blocking the activity of IL-1β, its receptor binding or production improves insulin signaling and action in human adipocytes. This is in parallel with a reduction in macrophage-stimulated proinflammatory profile and lipolysis. Targeting IL-1β may be beneficial for protecting against obesity-related insulin resistance at the tissue and systemic levels.

Adipose Tissue Remodeling in Obesity

Central obesity has a close link to the development of 'metabolic syndrome' manifested by insulin resistance, glucose intolerance, dyslipidemia and hypertension.[1] The metabolic derangements predispose to the development of type 2 diabetes and cardiovascular diseases.[1] Although the pathophysiology of obesity-associated metabolic disorders is complex, evidence suggests that chronic low-grade inflammation in white adipose tissue plays a role.[2-4] Adipose tissue is composed of mature adipocytes (∼50%) and other cells (∼50%) from the stromal vascular fraction (SVF) which contains preadipocytes, fibroblasts, endothelial cells and immune cells (i.e. macrophages, lymphocytes, mast cells, dendritic cells, eosinophils).[5,6] The plasticity of adipose tissue provides a mechanistic base for its pleiotropic functions that influence lipid, endocrine, and immune homeostasis. However, overnutrition in obesity triggers adipose tissue remodeling that the tissue becomes a site of inflammation. In addition to adipocyte hypertrophy, there is a marked accumulation of macrophages together with other immune cells in adipose tissue.[2,7,8] The proportion of macrophages in the SVF is estimated to be increased from ∼10% in lean to ∼40-50% in obese adipose tissue.[9] Furthermore, obesity induces a phenotypic switch from the M2 macrophages (producing anti-inflammatory cytokines) to the M1 macrophages (producing pro-inflammatory cytokines), associated with insulin resistance both in mice and humans.[10-12] Factors derived from macrophages also influence adipose tissue biology, such as inhibiting adipogenesis, modulating adipokine production, and mounting inflammatory responses.[13-18]

Macrophage-Adipocyte crosstalk on insulin signaling in adipose tissue

In addition to skeletal muscle and liver, adipose tissue is a key organ that responds to insulin action.[19] In obesity the lowered insulin sensitivity in adipocytes could stimulate lipolysis and fatty acid release into the circulation, leading to ectopic fat deposition and ultimately systemic insulin

resistance.[20] Insulin action requires the activation of insulin signaling pathway; IRS1, one of the major substrates of the insulin receptor, is essential to activate PI3K in response to insulin, which leads to the phosphorylation of protein kinase B (also known as Akt) resulting in an increase in GLUT4 transporters in the plasma membrane.[21] The enhanced macrophage-adipocyte crosstalk in obesity, including macrophage-derived factors, has been shown to disrupt insulin action in murine 3T3-L1 adipocytes.[22] However, whether it occurs in human adipose tissue together with the potential mediators and mechanisms are largely unknown. Our recent study examined the impact of signals derived from human macrophages on insulin signaling in human adipocytes.[23] We observed that macrophage-derived factors impair insulin signaling in human adipocytes as macrophage-conditioned (MC) medium inhibited gene and protein expression of insulin signaling molecules, including IRS1, PI3K p85α, GLUT4 and the phosphorylation of Akt. In contrast, the expression and release of the proinflammatory markers (i.e. IL-6, IL-8, MCP-1, CCL-5) by adipocytes were markedly increased.

IL-1β and insulin resistance

Identification of the major factors that mediate the detrimental effect of macrophages on adipocytes is challenging but it may offer potential therapeutic targets. Several macrophage-secreted factors are implicated in metainflammation, including TNFα and IL-6. TNFα has been shown to induce insulin resistance in rodents and block insulin actions in 3T3-L1 adipocytes.[22, 24-26] Using human preadipocytes, neutralization of TNFα attenuated macrophage-stimulated increase in IL-6 mRNA while had a modest effect on adipogenic marker aP2.[16] In our recent study, simultaneously blocking TNFα and IL-1β had no additive effect on the expression of insulin signaling proteins.[23] IL-6 was found to be overexpressed in fat cells from insulin-resistant subjects and induce insulin resistance in 3T3-L1 adipocytes.[27] It remains to be investigated whether IL-6 acts as a key mediator in macrophage-adipocyte crosstalk. Macrophage-derived IL-1F6 and IL-1F8,

members of the IL-1 family, was reported to stimulate gene expression of IL-6 and IL-8 in mature human adipocytes albeit both are less potent than IL-1β.[28] The involvement of IL-1F6 and IL-1F8 in adipose tissue inflammation and insulin sensitivity in obesity is not yet known.

IL-1β, a major proinflammatory cytokine, is produced mostly by macrophages and biologically active IL-1β is formed through cleavage of pro-IL-1β by caspase-1 activated via the NLRP3 inflammasome.[29] IL-1β production by adipose tissue macrophages is caspase-1-dependent in humans.[30] Growing evidence suggests that IL-1β is critically involved in the translation of obesity-associated inflammation into insulin resistance in rodent models.[31,32] IL-1β is also released by human adipose tissue but primarily from the nonfat cells, and the release is enhanced in obesity.[33,34] High dose of IL-1β (20 ng/ml) has been shown to decrease protein expression of IRS-1 and GLUT4 mRNA in murine 3T3-L1 adipocytes.[35, 36] Our recent work demonstrated that in human adipocytes IL-1β at a lower dose (2 ng/ml) repressed insulin signal transduction by reducing the expression of signaling (i.e. IRS1, PI3K p85α, pAkt) and glucose transporter (GLUT4) proteins.[23] We also found in a previous study that macrophage-induced production of matrix metalloproteinase 1 and 3 by preadipocytes is mediated by IL-1β.[37] These findings suggest that IL-1β could have a central role in macrophage-adipocyte crosstalk which blocks insulin action in human adipose tissue.

IL-1β as a mediator of macrophage-adipocyte crosstalk

In our recent work, we showed that IL-1β is required for the inhibitory effect of macrophages on insulin signaling in human adipocytes.[23] Blocking IL-1β activity, with a neutralizing antibody, substantially reduced effects of MC medium on expression profile of genes involved in insulin signaling, insulin sensitivity and glucose metabolism in adipocytes. Furthermore, IL-1β depletion abolished macrophage-induced inhibition on expression of insulin signaling proteins (IRS1, PI3K p85α and GLUT4 and Akt phosphorylation) and glucose consumption,

suggesting that IL-1β blockade can restore insulin signal transduction in human adipocytes. This was supported by the data that inhibition of IL-1β receptor binding in adipocytes with an IL-1 receptor antagonist (IL-1Ra) restored expression of signaling and glucose transport proteins suppressed by MC medium. To substantiate the importance of IL-1β in MC medium, we used a caspase-1 inhibitor to block IL-1β production by macrophages. The protein expression of insulin signaling molecules was partially (for IRS1, PI3K p85α) or totally (for GLUT4) reversed in adipocytes exposed to the MC medium. This is in parallel with the attenuation of macrophage-stimulated proinflammatory profile and lipolysis.

Although the mechanisms by which IL-1β mediates macrophage-adipocyte crosstalk desensitizing insulin action remain to be clarified, local inflammation in adipose tissue could be vital.[4] It is evident that macrophage-derived factors potently stimulate the production of proinflammatory cytokines/chemokines (i.e. IL-6, MCP-1, CCL5, IL-8) by adipocytes as well as preadipocytes.[16,23,38] The overproduction of chemoattractants may promote monocyte migration and M1 macrophages polarization.[39-42] Cytokine IL-6 and TNFα are known to reduce insulin signaling and insulin-stimulated glucose uptake in 3T3-L1 adipocytes.[24-27] Interestingly, we observed that overproduction of proinflammatory markers can be largely reversed by antagonizing IL-1β activity, IL-1 receptors or blocking IL-1β production.[23] Thus, the detrimental effects of macrophage-derived IL-1β on insulin signaling in adipocytes could be mediated via upregulated inflammatory responses, especially over-production of proinflammatory cytokines/chemokines (**Fig. 1**).

Targeting IL-1β in obesity

In rodent models of obesity and diabetes, blocking IL-1β reduces hyperglycemia and tissue inflammation.[43-46] In patients with type 2 diabetes, IL-1β antagonism or IL-1 receptor antagonist (anakinra) also show beneficial effects on glucose control and β-cell function, with a reduction in circulating proinflammatory markers.[47-49] Since adipose tissue inflammation links
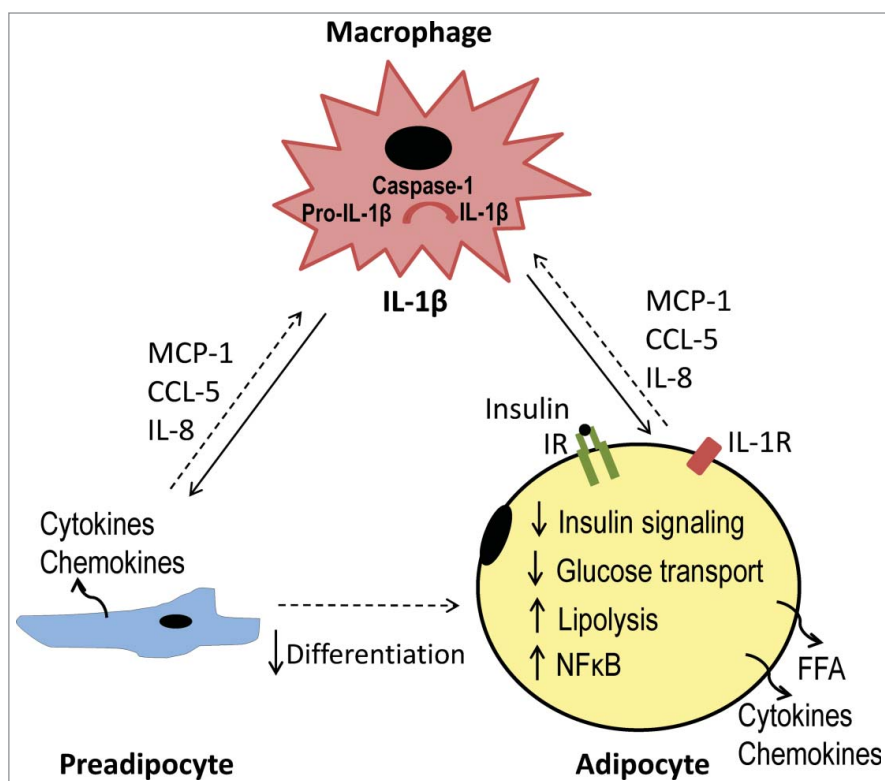
Figure 1. Schematic representation of IL-1β in the mediation of macrophage-induced adipocyte malfunction in obesity.

obesity to insulin resistance, studies on the tissue specific effects of IL-1β inhibition in humans are required. Targeting IL-1β might put a brake on the vicious cycle of macrophage infiltration and escalated inflammatory response in adipose tissue, thereby improving insulin sensitivity at tissue and also systemic levels.

Disclosure of Potential Conflicts of Interest

The author has no conflicts of interest to declare.

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