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Review

Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance ☆

Byung-Cheol Lee [a,b], Jongsoon Lee [a,*]

[a] The Joslin Diabetes Center and Department of Medicine, Harvard Medical School, Boston, MA 02215, USA
[b] Department of Internal Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Korea

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ABSTRACT

There is increasing evidence showing that inflammation is an important pathogenic mediator of the development of obesity-induced insulin resistance. It is now generally accepted that tissue-resident immune cells play a major role in the regulation of this obesity-induced inflammation. The roles that adipose tissue (AT)-resident immune cells play have been particularly extensively studied. AT contains most types of immune cells and obesity increases their numbers and activation levels, particularly in AT macrophages (ATMs). Other pro-inflammatory cells found in AT include neutrophils, Th1 CD4 T cells, CD8 T cells, B cells, DCs, and mast cells. However, AT also contains anti-inflammatory cells that counter the pro-inflammatory immune cells that are responsible for the obesity-induced inflammation in this tissue. These anti-inflammatory cells include regulatory CD4 T cells (Tregs), Th2 CD4 T cells, and eosinophils. Hence, AT inflammation is shaped by the regulation of pro- and anti-inflammatory immune cell homeostasis, and obesity skews this balance towards a more pro-inflammatory status. Recent genetic studies revealed several molecules that participate in the development of obesity-induced inflammation and insulin resistance. In this review, the cellular and molecular players that participate in the regulation of obesity-induced inflammation and insulin resistance are discussed, with particular attention being placed on the roles of the cellular players in these pathogeneses. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

Insulin resistance is the condition where the body does not respond appropriately to circulating insulin [1,2]. It associates commonly with obesity, hypertension, and cardiovascular disease and typically precedes the onset of Type 2 Diabetes (T2D). Insulin resistance occurs in several tissues, including the liver, muscle and adipose tissue (AT). The liver helps to maintain fasting glucose levels through gluconeogenesis and glycogenolysis. However, when the liver is insulin-resistant, the suppression of hepatic glucose production is impaired and thus gluconeogenesis and glycogenolysis continue at inappropriately high levels despite normal or high circulating glucose levels. AT and muscle are similarly affected by insulin resistance, although the problem here relates more to the impaired ability of insulin to promote glucose disposal. To compensate for the insulin resistance in these tissues, pancreatic β-cells produce more insulin. However, there is a limit to how much can be produced, and when this has been reached, the β-cells fail. T2D occurs when an inappropriately low level of insulin is produced in response to a given concentration of glucose.

At the cellular level, the molecular mechanism that underlies the development of insulin resistance is impairment in the insulin signaling pathway in insulin-responsive cells (adipocytes, myocytes, hepatocytes and β-cells). Normally, when insulin binds to the insulin

Abbreviations: ABCA, ATP-binding cassette transporter; AIM, Apoptosis inhibitor of macrophage; APC, antigen-presenting cell; ASC, apoptotic speck protein containing a caspase recruitment domain; AT, adipose tissue; ATM, AT macrophage; BLT, leukotriene B4 receptor; BM, bone marrow; BMT, bone marrow transplantation; Bregs, regulatory B cells; Casp1, Caspase 1; CCL5, Chemokine (C-C motif) ligand 5; CCR2, C-C chemokine receptor type 2; CLSs, crown-like structures; CTLs, cytotoxic T cells; CX3CR1, CX3C chemokine receptor 1; CXCL5, C-X-C motif chemokine 5; CXCR2, C-X-C motif receptor 2; DAMPs, Damage-associated molecular pattern molecules; DC, Dendritic cells; dsDNA, double stranded DNA; ECM, extracellular matrix; FABP, fatty-acid-binding protein; FFA, Free fatty acids; GFP, green fluorescent protein; GLUT4, Glucose transporter type 4; GPR120, G-protein coupled receptor 120; HFD, high fat diet; HMGB1, high-mobility group box 1; IKKb, inhibitor of κB kinase-β; IR, insulin receptor; JNKs, Jun N-terminal kinases; IRS, Insulin receptor substrate; KLF4, Krueppel-like factor 4; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MGL1, macrophage galactose-type lectin 1; MHC, Major histocompatibility complex; MPO, myeloperoxidase; NE, neutrophil elastase; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; NKT, Natural Killer T cell; Nlrp3, NOD-like receptor family, pyrin domain containing 3; NLS, nuclear localization sequence; PBMC, peripheral blood mononuclear cell; PKC, Protein kinase C; PPAR, peroxisome proliferator-activated receptors; PRRs, Pattern recognition receptors; RAGs, Recombination activating genes; RANTES, Regulated on Activation Normal T cell Expressed and Secreted; ROS, Reactive oxygen species; SOCS1, Suppressor of cytokine signaling 1; Sorbs1, Sorbin and SH3 domain-containing protein 1; SVC, stromal vascular cell; T2D, Type 2 Diabetes; TAMs, tumor-associated macrophages; TCRs, T cell receptors; TLR, Toll-like receptors; TNF, Tumor necrosis factors; Treg, regulator T cells; TZDs, thiazolidinediones

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* Corresponding author at: Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, USA. Tel.: +1 617 713 3422; fax: +1 617 309 2407.
E-mail address: jongsoon.lee@joslin.harvard.edu (J. Lee).

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receptor on these cells, the insulin receptor is autophosphorylated at its Tyr residues and its tyrosine kinase is activated [3,4]. The insulin receptor then phosphorylates tyrosine residues on the insulin receptor substrates (IRSs), which then serve as docking proteins for SH2-containing enzymes such as p85 subunit of PI-3 kinase or SHP2. This leads to linear signaling cascades that result in Akt activation. The activation of Akt induces the translocation of Glut4 and glycogen synthesis and thus plays an important role in metabolic signaling. Hence, disruption of this insulin signaling cascade can induce insulin resistance and is associated with the development of T2D. It is widely agreed in the field that obesity is a major cause of impaired insulin signaling and therefore the development of insulin resistance. However, it is not fully understood how obesity causes the development of insulin resistance. Many molecular mechanisms are proposed, including ER stress, oxidative stress, dysregulation of lipid homeostasis (including FFA homeostasis), mitochondrial dysfunction, hypoxia and others [5]. However, there are now many lines of evidence that suggest that obesity-induced inflammation may also be a key cause of insulin resistance. Recent studies in this field have also identified many cellular and molecular players that participate in the development of obesity-induced inflammation and insulin resistance.

2. Obesity-induced Inflammation

Inflammation is a series of cellular and molecular responses that serve to defend the body from infections or other insults. These responses also help the tissues that were damaged by the insults (and the immune responses that were induced by the insults) to recover. Inflammation has mainly been studied in infectious models but its dysregulation has also been implicated as a major cause of many diseases such as rheumatoid arthritis, atherosclerosis, asthma and other autoimmune diseases [6–8]. The main cellular players in inflammation are immune cells, which can be roughly divided into pro- and anti-inflammatory immune cells whose relative balance and functions tightly control the inflammation processes [9]. For example, when cells are infected by foreign bacteria or viruses, the danger signals produced by these infected cells are detected by surveilling immune cells, particularly neutrophils. The neutrophils then migrate into the local sites of infection, where they produce a series of chemokines that recruit other immune cells. Macrophages are recruited first, after which lymphocytes are recruited. The infiltrating immune cells then kill and remove the infected cells, after which the inflammation resolves and tissue healing starts. Finally, B cells mediate the transition from innate immunity to adaptive immunity. When inflammation is induced without infection, it is called sterile inflammation. In this case, the cells are mainly killed by necrosis and produce DAMPs such as HMGB1 and dsDNA that bind to PRRs such as TLRs, thereby initiating inflammation. Thus, in general, inflammation is often characterized by increased cytokine levels in the circulation and local sites of inflammation along with increases in the infiltrating immune cell numbers in the local sites. Acute inflammation is often defined as the presence of neutrophils at the sites of inflammation while chronic inflammation is generally defined as the infiltration of macrophages into the inflamed tissue.

While obesity-induced inflammation resembles the inflammation in classical immunity in many ways, it also differs from the latter in that it is a low-grade inflammation that produces much lower levels of circulating cytokines. It is also considered to be a chronic inflammation because it requires relatively long diet treatments (>8 weeks in animal models) before it becomes clearly discernible in the AT, which of all the various insulin-responsive tissues has the most severe obesity-induced inflammation (as characterized by the increased cytokine/chemokine expression and immune cell infiltration). Indeed, obesity-induced inflammation particularly resembles the inflammation observed in atherosclerosis, which is one of the complications of metabolic syndrome along with insulin resistance and lipid dysregulation [10]. Thus, obesity-induced inflammation may be a different kind of inflammation, namely one that is the result of overnutrition and stress pathways that drive abnormal metabolic homeostasis (e.g., high levels of lipid, FFA, glucose or ROS).

The role of inflammation in the development of obesity-induced insulin resistance was first suggested by the early studies on TNFα in the 1990s. These studies showed that when adipocytes were treated with TNFα, their insulin signaling was impaired, mainly because of changes in the transcription of insulin signaling molecules, in particular the insulin receptor, IRS-1, and Glut4 [11,12]. Animal studies also revealed that interventions that increased TNFα levels induced insulin resistance, and that the blocking of TNFα functions by genetic and pharmacological interventions improved obesity-induced insulin resistance [13–17]. Thus, these were the first studies to show that an inflammatory mechanism, namely the pro-inflammatory cytokine TNFα, can regulate obesity-induced insulin resistance *in vitro* and *in vivo*. While most of these studies focused on TNFα rather than on inflammation *per se*, they provided the novel concept that an immune pathway may regulate the development of obesity-induced insulin resistance.

Then, in the early 2000s, a series of epidemiological studies revealed that circulating inflammatory markers associate strongly with T2D and are risk factors for the development of future T2D [18–29]. These clinical but still observational studies were then supported by preclinical studies showing that obesity activates inflammation *via* the IKKβ/NFκB pathway and that inhibition of this pathway by genetic deletion of IKKβ or pharmacological inhibitors of this pathway (a high dose of salicylates or aspirin) improves obesity-induced insulin resistance [30,31]. Clinical studies then showed that when inflammation in insulin-resistant or T2D patients was suppressed by a high dose of aspirin or salsalate (a dimer of salicylate), the glycemic control of the patients improved, along with concomitant inhibition of NFκB activity in their PBMCs [32–35]. Numerous preclinical and clinical studies now strongly support the notion that obesity-induced inflammation plays an important role in the development of insulin resistance and T2D [36,37].

The next question was, "Which tissues/cells mediate the regulation of obesity-induced inflammation?" Two seminal papers by the Chen and Ferrante groups tested this question directly [38,39]. They showed that obesity increases AT macrophage (ATM) numbers and that ATMs, not adipocytes, produce the majority of cytokines in response to obesity. This made it clear that AT-infiltrated macrophages play a key role in the regulation of obesity-induced inflammation. Subsequently, many other types of immune cells were found in AT, most of which participate in the development of obesity-induced inflammation in AT as well. Hence, it is now generally accepted that tissue-resident immune cells play a major role in the regulation of obesity-induced inflammation and insulin resistance, like they do in classical immunity inflammation [40]. This notion is also strongly supported by studies examining the effects of genetic modulation of specific inflammatory mediators in immune cells [5,41,42].

3. Cellular players in obesity-induced AT inflammation

Obesity is defined as the expansion of fat, and obesity, especially in abdominal fat depots, is a risk factor for the induction of metabolic diseases. Therefore, to understand the molecular mechanisms that underlie the development of obesity-induced insulin resistance, the biology of AT has been studied extensively. In terms of glucose homeostasis, liver, AT and muscle are the major players; while liver maintains glucose levels between meals by producing glucose *via* glycogenolysis and gluconeogenesis, AT and muscle take up glucose after a meal. However, the AT only takes up a relatively small proportion of the glucose after a meal, although the insulin signaling and insulin-sensitive Glut4 regulation in AT have been studied

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