Published in final edited form as:

JPEN J Parenter Enteral Nutr. 2008 ; 32(6): 638–644. doi:10.1177/0148607108325251.

Adipose Inflammation, Insulin Resistance, and Cardiovascular Disease

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Abstract

Adiposity-associated inflammation and insulin resistance are strongly implicated in the development of type 2 diabetes and atherosclerotic cardiovascular disease. This article reviews the mechanisms of adipose inflammation, because these may represent therapeutic targets for insulin resistance and for prevention of metabolic and cardiovascular consequences of obesity. The initial insult in adipose inflammation and insulin resistance, mediated by macrophage recruitment and endogenous ligand activation of Toll-like receptors, is perpetuated through chemokine secretion, adipose retention of macrophages, and elaboration of pro-inflammatory adipocytokines. Activation of various kinases modulates adipocyte transcription factors, including peroxisome proliferator-activated receptor- γ and NF κ B, attenuating insulin signaling and increasing adipocytokine and free fatty acid secretion. Inflammation retards adipocyte differentiation and further exacerbates adipose dysfunction and inflammation. Paracrine and endocrine adipose inflammatory events induce a local and systemic inflammatory, insulin-resistant state promoting metabolic dyslipidemia, type 2 diabetes, and cardiovascular disease. Developing therapeutic strategies that target both adipose inflammation and insulin resistance may help to prevent type 2 diabetes and cardiovascular disease in the emerging epidemic of obesity.

Keywords

type 2 diabetes; insulin resistance; adiposity-associated inflammation; adipose tissue; insulin; fatty acids

Obesity, particularly visceral obesity, is closely linked to the development of the metabolic syndrome, type 2 diabetes mellitus, and atherosclerotic cardiovascular disease (CVD).¹ Activation of innate immune pathways in adipose tissue has been proposed to link obesity to insulin resistance (IR) and atherosclerosis. Recruitment and infiltration of adipose tissue macrophages (ATMs) lead to adipocyte inflammation.^{2,3} In this environment, a variety of endogenous and exogenous innate Toll-like receptor (TLR) antigens may promote a local metabolic endotoxemia and maintain adipocyte dysfunction and IR.⁴ Inflammatory adipose tissue is also a critical player in systemic IR through secretion of various adipocytokines⁵ and free fatty acids (FFAs)⁶ that regulate hepatic, skeletal muscle, and vascular insulin signaling. Finally, several chemokines, cytokines, kinases, and transcription factors have

been implicated in adipose inflammation, systemic IR, and a chronic inflammatory atherogenic state⁷ that contributes to type 2 diabetes and atherosclerosis.

Inflammation Modulates Adipose Functions

Preadipocytes

Preadipocytes have the capacity for phagocytosis and cytokine secretion.⁸ Lipopolysaccharide (LPS) induces chemokine secretion from and TLR expression in preadipocytes, demonstrating their capacity to recruit macrophages.⁹ This inflammatory response also contributes to IR in adipocytes.⁹ As preadipocytes undergo differentiation, their inflammatory capacity diminishes.⁹ Thus, inflammatory modulation of adipocyte differentiation plays an important role in local and systemic inflammation and IR (Table 1).

Innate Immunity and TLR4

TLR4 is an LPS receptor, also activated by long-chain fatty acids (FAs), that transduces cytokine expression.⁴ TLR4 can signal via MyD88 to activate NF κ B signaling or via an MyD88-independent pathway to induce interferon-regulatory genes.¹⁰ Activation of TLR4 in adipocytes induces NF κ B target genes and decreases Akt and GSK3 β phosphorylation, key mediators of insulin signaling and glucose uptake.¹⁰ Tsukumo et al¹¹ showed that a loss-of-function mutation in TLR4 protects mice from diet-induced obesity and IR. Compared with control conditions, a high-fat diet induced smaller fat depots, less adipose macrophage infiltration, lower FFAs, and normal insulin pathway phosphorylation as well as lower cytokines, blood glucose, and hepatic triglycerides in TLR-deficient mice.¹¹ TLR4 and its adaptor proteins, MyD88 and interleukin-1 receptor–associated kinase (IRAK-1), are also important in vascular inflammation and IR.¹² Not surprisingly, endotoxemia induces IR in vivo.^{4,13} Indeed, our group reported that experimental human endotoxemia promotes adipose inflammation and alters adipokine function coincident with systemic IR.¹⁴ Thus, TLR4 is a critical player in inflammation, IR, and vascular injury.

Recruitment and Actions of ATMs

ATMs play an important role in adipose inflammation and IR as well as in adiposity and type 2 diabetes.² There are 2 different populations of ATMs—the constitutive or resident ATMs and the short-lived or recruited ATMs.^{15,16} Resident ATMs assist with homeostasis and tissue remodeling, but in obese mice, they shift toward the classical, pro-inflammatory M1 (CCR2+) phenotype.¹⁷ A high-fat diet increases circulating M1 (CCR2+) monocytes^{15,17} and promotes their recruitment and retention in adipose tissue.^{15,16} Recruited ATMs induce adipocyte inflammation, promote adipose neovascularization, and interfere with insulin signaling.¹⁸ When mixed with macrophage media, adipocytes demonstrate increased inflammatory genes, adhesion to monocytes, increased NF κ B activity, and decreased insulin-stimulated glucose uptake.³ Thus, ATM-secreted factors cause inflammation in adipocytes, and adipocyte/macrophage cross-talk contributes to IR.³

Chemokines in Adipose Inflammation, Insulin Resistance, and Atherosclerosis

Chemokines and their receptors play a critical role in ATM recruitment to adipose tissue. Monocyte chemoattractant protein-1 (MCP-1) is strongly implicated in ATM recruitment, adipose expansion and remodeling, and angiogenesis.^{19,20} MCP-1 is overexpressed in obese rodents and obese diabetic humans, and it is associated with macrophage infiltration and IR.^{16,20} Furthermore, MCP-1 deficiency or inhibition of MCP-1 expression in obese mice ameliorates IR and reduces ATMs.¹⁹ CCR2, the MCP-1 receptor, also plays a role in adipose inflammation. In fact, on a high-fat diet, CCR2 knockout mice had reduced ATMs coincident with less obesity, increased insulin sensitivity and circulating adiponectin, and lower inflammatory cytokines and hepatic triglycerides.²¹ RANTES (which stands for

“regulated on activation, normal T cell expressed and secreted”), a recently discovered chemokine, plays a role in T-cell chemotaxis and is found to be elevated in the adipose tissue of obese mice and humans.²² Both MCP-1 and RANTES are up-regulated in atherosclerotic lesions,²³ and attenuation of their signaling inhibits macrophage foam-cell formation and lesion development.^{24,25} Overall, several chemokines²⁶ play critical roles in obesity, IR, and atherosclerosis.

Adipokines in Inflammation, Insulin Resistance, and Atherosclerosis

Adipokines provide an important link between obesity and IR. Adiponectin is a unique adipokine that is inversely related to the metabolic syndrome, type 2 diabetes, and atherosclerotic CVD.²⁷ Adiponectin increases FA oxidation while reducing glucose production in liver, and ablation of the gene in mice induces IR, type 2 diabetes, and atherosclerosis.²⁸ Adiponectin is also anti-inflammatory; it suppresses tumor necrosis factor (TNF) actions in nonalcoholic fatty liver disease and inhibits NF κ B in and monocyte adhesion to endothelial cells.²⁹ Resistin, another adipokine, is secreted by adipocytes in rodents but is restricted to immune cells in humans.³⁰ Human resistin is generated by infiltrating inflammatory cells in human adiposity and can stimulate synthesis and secretion of cytokines in adipocytes and endothelial cells.³¹ Leptin, a well-known adipokine, normally functions centrally to suppress appetite, but most obese patients are leptin resistant with increased circulating leptin.³² In obesity, hyperleptinemia contributes to inflammation through modulation of T-cell and monocyte functions.^{33,34} A role for retinol-binding protein 4 (RBP-4; a more recently described adipokine) in IR has been proposed, and RBP-4 expression in adipose is linked to inflammation.³⁵

Visfatin is a novel adipokine that is increased during the development of obesity, is pro-inflammatory,³⁶ and has an insulin-mimetic effect via binding to the insulin receptor.³⁷ A member of the lipocalin family, lipocalin-2, also known as neutrophil gelatinase-associated lipocalin,³⁸ modulates inflammation and is another adipokine that is elevated in the adipose tissue of obese mouse models³⁹ and in the plasma of obese and insulin-resistant humans.⁴⁰ In vitro studies suggest that lipocalin-2 induces IR in adipocytes and hepatocytes.³⁹ The plasma level of another member of the lipocalin family, lipocalin-type prostaglandin D synthase, serves as a biomarker of coronary atherosclerosis.⁴¹ Thus, multiple adipose-secreted factors that modulate systemic IR are regulated by inflammatory signals and in turn have a significant impact on innate immune and vascular inflammation.

Free Fatty Acids

Nutritional FFAs modulate the inflammatory response, particularly via NF κ B activity, and promote IR.^{6,42} Further-more, inflammatory modulation of adipocyte differentiation increases FFA release. Mechanisms of FFA-associated IR include protein kinase C (PKC) activation, endoplasmic reticulum stress, and increased oxidative burden.⁴³ FFAs inhibit insulin receptor substrates (IRSs) and induce IR in skeletal muscle and liver.⁶ Increased FFA flux from adipose tissue to liver causes hepatic IR by increasing gluconeogenesis, glycogenolysis, and glucose-6-phosphatase expression and activity⁶ and by enhancing lipogenesis and triglyceride synthesis attributable to activation of the transcription factor sterol-CoA regulatory element binding protein.⁶ Finally, FFAs cause endothelial IR and damage by impairing insulin and nitric oxide-dependent signaling,⁴⁴ thus contributing to the vascular injury observed in adiposity.

Adipose Cytokines Promote Insulin Resistance, Atherosclerosis, and Thrombosis

TNF- α is increased in adipose tissue and in the circulation in obese, insulin-resistant, and atherogenic states.^{45,46} In adipocytes and skeletal muscle, TNF- α inhibits tyrosine phosphorylation of IRS-1, which decreases insulin signaling.^{47,48} TNF- α receptor deficiency

protects against IR.^{47,49} In humans, TNF- α infusion decreases insulin sensitivity and increases phosphorylation of extracellular signal-regulated kinase-1/2 (ERK-1/2), c-Jun N-terminal kinase (JNK), and serine 312 on IRS-1.^{50,51} Interleukins (ILs) have also been implicated in obesity and IR. IL-6 is elevated in obesity and is increased in the portal circulation, thereby stimulating hepatic production of acute-phase reactants such as C-reactive protein.⁵² However, the role of IL-6 in IR remains controversial, and it may in fact be protective.⁵⁰ IL-18 is an inflammatory cytokine in the IL-1 family⁵³ that is elevated in obesity and is an independent predictor of CVD.^{54,55}

Several adipose-secreted factors not only are associated with inflammation but also promote hypercoagulability and thrombosis. Plasminogen activator inhibitor-1 (PAI-1) is a regulatory serine-protease inhibitor that decreases fibrinolysis⁵⁶ and correlates well with visceral adiposity and hyperinsulinemia.⁵⁷ PAI-1 knockout mice are protected against obesity and IR, likely secondary to maintenance of peroxisome proliferator-activated receptor- γ (PPAR- γ) and adiponectin expression.⁵⁸ Activation of the rennin-angiotensin system (RAS) in adipocytes up-regulates PAI-1 expression through the angiotensin type I receptor,⁵⁹ and hence blockade of the RAS may help to ameliorate PAI-1-related obesity and IR.

Molecular Mechanisms of Inflammatory Adipose Dysfunction and Insulin Resistance

The Insulin Signaling Pathway

Inflammation and adiposity cause IR by interfering with insulin signaling. Insulin receptor substrates are central molecular targets for inflammatory effects. Tyrosine phosphorylation of IRSs is important for normal insulin signal transduction. Sustained endotoxemia in a rat model decreases tyrosine phosphorylation of IRSs and decreases activation of PI3 kinase.⁶⁰ In mice, inflammatory serine 307 phosphorylation of IRS-1 interferes with insulin signaling⁶¹ (Figure 1).

Kinases and Regulatory Phosphorylation

Pro-inflammatory cytokines induce phosphorylation of diverse kinases. NF κ B drives transcription of inflammatory cytokines and contributes to IR in the setting of obesity and a high-fat diet.⁶² Normally, NF κ B is inhibited by I κ B α and therefore remains in the cytoplasm in an inactive state.⁶² With the appropriate stimuli, I κ K β (a serine kinase) is activated, which phosphorylates and degrades I κ B α , and this frees up NF κ B to enter the nucleus.⁶² I κ K β also interferes with insulin signaling by phosphorylating IRS-1.⁶² I κ K β overexpression increases NF κ B activity and decreases insulin signaling, whereas I κ K β deficiency increases insulin sensitivity.⁶²

The mitogen-activated protein kinase (MAPK) family comprises another set of kinases including JNK, p38 MAPK, and ERK. JNK isoforms couple inflammatory and metabolic signals, are activated through TNF- α signaling, and can phosphorylate serine 307 on IRS-1.⁶³ Another MAP kinase family member, p38 MAPK, contributes to adipocyte IR by interfering with genes involved in insulin signaling, including GLUT-4 and phosphoinositide phosphatase.⁶⁴ ERKs phosphorylate IRS-1 at a couple of serine residues.⁴³ In obesity, JNK-1, p38 MAPK, and ERK2 levels and activation are induced in visceral adipose, suggesting depot-specific roles in IR.⁶⁵

PKC- θ is another pro-inflammatory kinase implicated in IR. FFA metabolites activate PKC- θ , which increases serine 307 phosphorylation of IRS-1 and decreases insulin signaling.^{7,43} Human IRAK-1, homologous to mouse pelle-like kinase, is a serine/threonine kinase

activated by cytokines that phosphorylates JNK, I κ B β , and NF κ B and reduces insulin action.⁶⁶

Negative Feedback Regulator—Suppressor of Cytokine Signaling Proteins

Suppressor of cytokine signaling (SOCS) family proteins are increased by inflammatory cytokines.⁶⁷ SOCS proteins target cytokine tyrosine kinase receptor signaling in a negative feedback loop.⁶⁷ However, SOCS proteins are elevated in insulin-resistant tissues and attenuate signaling via the insulin receptor (InsR), also a tyrosine kinase.⁶⁷ SOCS proteins impair InsR signaling in 2 ways: by binding directly to IRSs, thus blocking InsR-mediated tyrosine phosphorylation,⁶⁷ and by promoting ubiquitination and degradation of IRSs.⁶⁸ Thus, SOCS proteins are key mediators of inflammatory IR and adipose dysfunction, although limited data are available in human disease.

Inflammation Modulates Transcription Factors That Regulate Adipocyte Differentiation

Transcription factors are crucial regulators of adipose differentiation and insulin sensitivity; they are the common final integration of many of the inflammatory pathways outlined above. PPAR- γ , the master regulator of adipogenesis, is regulated by serine phosphorylation and is attenuated in insulin-resistant states and by activation of inflammatory pathways.^{69,70} GATA2, another transcription factor regulated by serine phosphorylation, inhibits adipogenesis.⁷¹ Adipocyte IR prevents insulin-induced GATA2 phosphorylation, facilitating GATA2 inhibition of adipogenesis.⁷¹ FOXO1 is another transcription factor that also inhibits adipogenesis.⁷² Insulin negatively regulates FOXO1 activity via phosphorylation,⁷³ whereas Sirt2 plays a role in inhibiting adipocyte differentiation by deacetylating and activating FOXO1.⁷⁴ Recently, several additional transcription factor families that are regulated by inflammation, including bone morphogenic proteins^{75,76} and interferon regulatory factors,⁷⁷ have been identified as important regulators of adipocyte differentiation and adipose functions. These data underscore the profound inflammatory modulation of transcription factor regulation of adipose differentiation and secretory/metabolic functions that affect IR and CVD.

Implications for Humans

Increased CVD risk is found in patients who have chronic, low-grade inflammation and who are also insulin resistant. The mechanisms of adipose inflammation and the related systemic insulin-resistant, atherogenic inflammatory state are complex. Visceral adiposity and its inflammatory dysregulation are strongly implicated in the genesis of this milieu.⁷⁸ Perhaps anti-inflammatory therapeutic interventions will prove successful in reducing metabolic and vascular complications. In fact, lifestyle changes including exercise, weight loss, and reduction of visceral adiposity are associated with decreased inflammatory markers,⁷⁹ improved endothelial function, and decreased CVD risk.⁸⁰ Pharmacological approaches that target adipose inflammation warrant investigation but require specific proof of concept. PPAR- γ agonists, in fact, promote adipocyte differentiation and reduce adipose and systemic inflammation while improving insulin sensitivity.⁶⁹ However, controversy surrounds their effects on atherosclerotic CVD.⁸¹ Modulation of angiotensin and its receptors, already established to reduce CVD,⁸² provides an alternative strategy for modulation of adipose inflammation and IR but requires evidence of antiinflammatory action in human adipose. High-dose salicylates, long used in inflammatory disorders, inhibit IKK β ⁸³ and may provide significant proof that a targeted antiinflammatory strategy in humans reduces adipose inflammation and IR as well as atherosclerosis. In fact, such proof-of-concept trials are ongoing in clinical research programs sponsored by the National Heart, Lung, and Blood Institute (ClinicalTrials.gov Identifier: NCT00258128 and NCT00624923).

Conclusion

This article reviews recent data regarding mechanisms of adiposity-associated inflammation and IR, which play a pivotal role in the metabolic and cardiovascular consequences of obesity. The initial insult may occur through recruitment of macrophages and innate immune antigen activation of TLRs, which can be perpetuated through secretion of chemokines, retention of macrophages in adipose, and secretion of adipocytokines. This inflammatory milieu induces adipocyte inflammatory cascades, such as the NF κ B pathway, via activation of various kinases, and this modulates adipocyte transcription factors, attenuates insulin signaling, and increases pro-inflammatory adipocytokines and FFAs. Inflammatory attenuation of adipocyte differentiation further exacerbates adipose dysfunction. These paracrine and endocrine adipose inflammatory events induce a systemic inflammatory, insulin-resistant, atherogenic state and metabolic dyslipidemia, resulting in type 2 diabetes and CVD. Application of therapeutic strategies that target both adipose inflammation and IR may be required to prevent and treat type 2 diabetes and atherosclerotic CVD in the emerging epidemic of obesity.

Acknowledgments

Financial disclosure: This research was partially funded by a Clinical and Translational Science Award (RFA-RM-06-002) from the National Center for Research Resources, National Institutes of Health (NIH; Bethesda, MD); a Diabetes Endocrinology Research Award (P30 DK-019525) from NIH to the University of Pennsylvania; R01 HL-073278, R01 DK-021224, and P50 HL-083799 from NIH (SCCOR); and a W. W. Smith Charitable Trust award (West Conshohocken, PA; grant H0204), all to MPR.

The 2008 Intersociety Research Workshop: Nutrition and Inflammation: Research Makes the Connection, was supported by grant number U13DK064190 from the National Institute of Diabetes and Digestive and Kidney Diseases. The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.

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Figure 1.

Macrophage–adipocyte interplay in adipose tissue. Adipocytes secrete chemokines, which attract macrophages to adipose tissue. Binding of fatty acids (FAs) and innate antigens to Toll-like receptors (TLRs) on macrophages and adipocytes activates NFκB, modulating cytokine and adipokine biosynthesis and secretion. Adipocytokines can then bind to receptors on adipocytes and, via kinases, activate NFκB to stimulate suppression of cytokine signaling (SOCS) protein transcription. Kinases, via direct phosphorylation, and SOCS proteins, via insulin receptor substrate (IRS) binding and degradation, interfere with insulin signaling and prevent GLUT-4 translocation, leading to insulin resistance. Adipose inflammation also retards adipocyte differentiation, promoting a pro-inflammatory, insulin-resistant preadipocyte phenotype. Inflammatory modulation of adipocytokine and FA production and secretion results in hepatic, skeletal muscle, and vascular insulin resistance; metabolic dyslipidemia; and a systemic pro-inflammatory, atherogenic state. Adipokines (ie, leptin, resistin, lipocalin-2, etc); cytokines (ie, tumor necrosis factor [TNF]-α, interleukin-6 [IL-6], interleukin-18 [IL-18], plasminogen activator inhibitor-1 [PAI-1], etc); chemokines (ie, monocyte chemoattractant protein-1 [MCP-1]; regulated on activation, normal T cell expressed and secreted [RANTES]; fractalkine) and chemokine receptors (CCRs); kinases (ie, c-Jun N-terminal kinase [JNK], extracellular signal-regulated kinase [ERK], protein kinase C-θ [PKC-θ], p38 mitogen activated protein kinase [MAPK], phosphoinositide 3-kinase [PI3K], v-akt murine thymoma viral oncogene homolog 1 [AKT]). InsR, insulin receptors.

Table 1**Adipose Inflammatory Functions in Insulin Resistance and Cardiovascular Disease**

Component	Function	Key References
Preadipocytes	Macrophage-like, pro-inflammatory, interfere with adipocyte insulin signaling.	9
Innate immunity	Innate antigens and TLRs transduce adipocyte inflammation; mediate diet-induced obesity and insulin resistance.	4, 10, 11
ATMs	Resident ATMs shift toward pro-inflammatory phenotype in obesity, whereas high-fat diet recruits ATMs (CCR2+) via chemokines; ATMs contribute to adipose inflammation and insulin resistance.	15–18
Chemokines	CCL2 (MCP-1) and its receptor, CCR2, play a key role in diet-induced recruitment and retention of ATMs, obesity, and insulin resistance; RANTES promotes T-cell chemotaxis and is elevated in obesity.	19, 20, 22
Adipokines	Adipose inflammation regulates adiponectin, resistin, leptin, RBP-4, visfatin, and lipocalin-2 production; adipokines modulate systemic insulin signaling, hepatic lipoprotein production, innate immunity, and vascular inflammation.	5, 29
FFAs	Adipose inflammation induces higher adipocyte FFA production; FFAs induce insulin resistance in skeletal muscle and liver, modulate lipoprotein production, and impair endothelial functions.	6
Cytokines	Adipose inflammation increases local and systemic cytokine production, which induces adipocyte insulin resistance, systemic insulin resistance, endothelial dysfunction, and vascular inflammation.	45, 52, 53, 57

TLR, Toll-like receptor; ATM, adipose tissue macrophage; MCP, monocyte chemotactic protein; RANTES; regulated on activation, normal T cell expressed and secreted; RBP, retinol binding protein; FFA, free-fatty acid.