Adipose tissue signaling by nuclear receptors in metabolic complications of obesity

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Abbreviations: AP-1, activator protein 1; ATMs, adipose tissue macrophages; BAT, brown adipose tissue; Cap, Cbl-associated protein; nuclear receptors, metabolic syndrome, insulin resistance, obesity, adipocyte, adipokines, macrophage, inflammation, PPAR

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In recent years white adipose tissue inflammation has been recognized to be associated with obesity. Adipocytes and adipose tissue associated macrophages (ATMs) secrete bioactive molecules, including adipokines, chemokines/cytokines and free fatty acids that modulate the development of low-grade inflammation and insulin resistance responsible for obesity-related metabolic and cardiovascular diseases. Nuclear receptors, notably peroxisome-proliferator-activated receptors, are sensors of dietary lipids and control transcriptional programs of key metabolic and inflammatory pathways in adipocytes and macrophages. This review focuses on mechanisms by which nuclear receptors maintain white adipose tissue homeostasis. The identification of ATMs as active players in the initiation of chronic inflammation and the links between inflammatory signaling and metabolic dysfunction will be presented, followed by discussion of recent evidence for nuclear receptors in ATMs function, with an emphasis on the paracrine interaction between adipocytes and ATMs.

Introduction

A primary role for adipocytes is energy storage. Adipocytes can synthesize energy rich triacylglycerol from glucose or simply store fats transported by very low-density lipoproteins. The compact, anhydrous fat droplets holding triacylglycerol within adipocytes can conveniently sustain energy requirements over periods of starvation that likely affected our hunter-gatherer ancestors. However, the discovery of leptin in 19941 has shifted our vision of adipose tissue toward that of an active endocrine tissue.2 To date, many more adipocyte-secreted molecules have been identified. Collectively termed adipokines, these molecules regulate whole body homeostasis through endocrine3 and autocrine/paracrine activities.4 It is now also clear that the maladaptation of adipocytes to over-nutrition in obesity is causative to metabolic dysfunction. Dietary overload and an inactive lifestyle are modern phenomena leading to excess accumulation of body fat responsible for a chronic inflammatory disease that is tightly connected to insulin resistance, thereby linking obesity with its metabolic complications.5 This inflammation does not rely on the classic instigators of immune responses, e.g., infection or tissue injury, which initiate the recruitment of leukocytes toward affected tissues. Rather, it is an immunological response to adipose tissue malfunction. This type of inflammation is referred to as para-inflammation6 and is dependent on white adipose tissue (WAT) infiltration by macrophages.7,8 Mechanisms involved in the self-maintenance of this inflammatory state in response to chronic caloric overload are currently being investigated. Evidence suggests that adipocytes and adipose tissue resident macrophages (ATMs) secrete bioactive molecules including inflammatory and anti-inflammatory cytokines that could be related to the development of low-grade systemic inflammation and insulin resistance.9,10

Studies have shown that nuclear receptors are intracellular points of convergence for metabolism and inflammation. In the past decade, several nuclear receptors have been identified as sensors for dietary lipids that regulate transcriptional programs of key metabolic pathways. Recent findings further highlighted a role for nuclear receptors in the pathophysiology of the metabolic syndrome through the control of adipocyte function and ATM activation. This review will discuss the mechanisms by which nuclear receptors modulate WAT signaling and how the activities of nuclear receptors in WAT relate to the metabolic complications of obesity. A report of the link between chronic inflammation,
ATMs and metabolic diseases will be presented, followed by discussion of the involvement of nuclear receptors in maintaining homeostasis within WAT. We will also review recent evidence for nuclear receptors in ATM function, focusing on the paracrine interaction between adipocytes and ATMs.

**Adipose Tissue: An Important Source of Metabolic Inflammation**

An increase in fat mass as a result of sustained positive energy balance correlates with changes in endocrine and metabolic functions. Notably, WAT from obese individuals show increases in inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), inducible nitric oxide synthase (iNOS), tumor growth factor β1 (TGF-β1), and monocyte chemotactic protein-1 (MCP-1). In addition to adipocytes, the stromal-vascular fraction of WAT contains a heterogeneous cellular population, including endothelial cells, pre-adipocytes/ﬁbroblasts, macrophages and other immune cells (e.g., T cells and eosinophils). In 2003, two reports provided the first evidence that obesity is associated with increased presence of macrophages in WAT in mouse models of obesity. These studies identiﬁed gene transcripts encoding proteins distinctive of macrophages in perigonadal fat tissues. Gene expression in macrophage and non-macrophage cells from WAT also showed that ATMs are the main source of TNF-α and other pro-inﬂammatory molecules in adipose tissue. Based on the results in mice, histological studies in human showed that the quantity of macrophage in WAT correlated positively with body mass index and adipocyte size. Follow-up studies demonstrated that human visceral WAT, the accumulation of which is associated with alteration in lipid proﬁle and insulin sensitivity, also contains macrophages in greater number in obesity. In paired biopsies obtained from obese adults during bariatric surgery, there were twice as many macrophages in visceral as in subcutaneous WAT. Similar to the results derived from mouse models, studies of human WAT showed that non-adipocyte cells were the main sources of inﬂammatory cytokines. Analysis of adipose tissue in obesity shows the convergence of macrophages on adipocytes of necrotic appearance, described as “crown-like structures.” Collectively, these ﬁndings suggest that WAT in the obese state is associated with sustained inﬂammation, characterized by excessive macrophage inﬁltration.

**The M1/M2 Dichotomy of Adipose Tissue Macrophages**

Identification of different subsets of macrophages in WAT represents a second signiﬁcant ﬁnding in understanding the pathogenesis of metabolic diseases. Macrophages are heterogeneous, with phenotypic differences associated with differential expression patterns of cytokines, surface markers and metabolic enzymes. Two separate states are commonly used to deﬁne macrophage activation, although they likely represent extremes of a continuum. Pro-inﬂammatory mediators and microbial triggers, such as the bacterial lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria, induce M1 or “classically activated” macrophages. M1 macrophages produce pro-inﬂammatory cytokines (e.g., TNF-α, IL-6 and IL-1β) and reactive oxygen species such as nitric oxide via activation of iNOS. Whereas the M1 macrophages are essential for removal of pathogens, long-lasting activation of this phenotype is considered to be deleterious to body homeostasis. In contrast, the M2 or “alternatively activated” macrophage produces IL-10 to suppress inﬂammation (for reviews see refs. 26 and 27). Following the reports that obesity increases macrophage inﬁltration in WAT, it was shown that diet-induced obesity is also associated with a change in the polarization of ATMs from the M2 state in lean mice to a predominantly M1 proinflammatory state. Therefore, the balance between M1 and M2 macrophages controls the progression of immune responses in WAT, which is thought to have a key role in the development of metabolic diseases (Fig. 1).

**Links Between Inflammation and Insulin Resistance**

Evidence supporting pro-inflammatory signaling-dependent induction of metabolic dysfunction preceded our understanding of adipocyte/macroraphage interactions. Data exists showing a positive correlation between macrophage inﬁltration of visceral fat and the severity of hepatic damage in obese patients. Speciﬁc knockout experiments in the myeloid lineage provide insights into the involvement of macrophages in the anomalies of the metabolic syndrome. However, these studies did not specify ATM contributions.

*Suppression of inﬂammation in obesity improves insulin resistance.* Hotamisligil et al. ﬁrst observed that WAT and circulating TNF-α protein levels were elevated in obese rodents, as compared with lean controls. Neutralization of TNF-α action with a recombinant soluble TNF-α receptor in obese fat/βa rats caused an increase in peripheral glucose uptake in response to insulin. The deﬁnitive proof that inﬂammation and increased cytokine levels in obesity are responsible for insulin resistance was obtained four years later using genetic models of mice lacking TNF-α or TNF-α receptors. Absence of TNFα signaling resulted in improved insulin sensitivity in both diet-induced obese mice and the ob/ob model of obesity. Inflammatory signaling pathways, including that of TNFα, are mediated by several protein kinases, such as IkB kinase (IKKs) and c-Jun N-terminal kinases (JNKs). Mice lacking Ikβ-β, a regulator of inﬂammatory responses through activation of NFkB (nuclear factor kappa B), in myeloid cells are protected from insulin resistance. Studies on JNK1 action during development of insulin resistance support a common mechanism through which JNK1 activation in insulin target cells directly interferes with insulin signaling. Jnk1-/- mice exhibit a lean phenotype, are protected from diet-induced obesity and have reduced expression of pro-inﬂammatory mediators such as IL-6, TNFα, IL-1β, migration inhibitor factor and MCP-1, compared with wild-type mice. Subsequent work demonstrated that removal of Jnk1 in the non-hematopoietic tissues protects mice from insulin resistance caused by high fat diet, partly through decreased adiposity. Jnk1 deletion from
The Origin of Metabolic Inflammation in Obesity

The mechanism underlying metabolic dysfunction/obesity induced chronic inflammation is still unclear. The so-called “portal hypothesis” proposes that increased lipolysis in the visceral fat of obese individuals exposes the liver to high concentrations of free fatty acids (FFA), eventually contributing to liver insulin resistance. Similar effects from FFA are seen in other tissues, such as muscle and pancreas (a process termed lipotoxicity, for a review see ref. 39). FFA have been shown to directly activate the macrophage M1 response in vitro (Fig. 2). For example, toll-like receptor 4 (TLR4), the receptor for LPS, was shown to mediate the effects of FFA on inflammation. The capacity of FFA to induce inflammatory signaling and cytokine expression in adipocytes and macrophages is decreased in the absence of TLR4. Furthermore, Tlr4−/− mice are protected from diet-induced insulin resistance. While it is known that visceral WAT has higher levels of lipolysis and contains more ATMs than abdominal subcutaneous WAT,11–13 recent studies have characterized the effects of weight loss and fasting on ATMs in mice and identified a role for lipolysis in macrophage recruitment. First, increases in ATM number correlate with plasma concentrations of FFA and adipose tissue lipolysis. Second, dietary and genetic modifications aimed at reducing lipolysis or weight gain decreased ATM accumulation. Finally, macrophage/adipocyte co-cultures suggested that local lipid fluxes are important regulators of ATM activation. Taken together, these studies are consistent with the possibility that within WAT, pro-inflammatory adipokines and FFA play a major role in the initiation of chronic inflammation and metabolic dysregulation that are observed in obesity (Fig. 2).

Lipid Sensing Nuclear Receptors in Adipose Tissue Homeostasis

Although the findings discussed above strongly suggest a link between increased adiposity, systemic inflammation and insulin...
resistance through the activation of ATMs, a critical unanswered question is whether ATM activation can be modulated pharmacologically. Since certain nuclear receptors act as sensors for dietary fats and are also involved in the regulation of inflammation, they represent attractive druggable targets to control metabolic inflammation and associated diseases. We will focus on members of the fatty acid sensing peroxisome proliferator-activated receptor (PPAR) family, as they are known to regulate adipocyte function and macrophage immune response and as such, play an important role in WAT homeostasis.

The Transcriptional Action of Nuclear Receptors

Nuclear receptors are ligand-activated transcription factors responsible for the control of diverse biological processes. The biochemical studies that first described the action of steroid hormones provided a general mode of action for a large family of nuclear receptors responsive to a variety of lipophilic signaling molecules, including steroids, retinoids, dietary lipids and xenobiotics. Most of the receptors contain a conserved structure with a heterogeneous N-terminal domain, a central DNA binding domain and a C-terminal ligand-binding domain, responsible for ligand binding, receptor dimerization and ligand-dependent activation of transcription. Several members in this superfamily, such as PPARs, liver X receptors (LXRs), farnesoid X receptor (FXR) and the retinoid-related orphan receptors (RORs), are thought to be metabolic sensors, as their ligands include fatty acids and cholesterol derivatives. Activation of these receptors, notably PPARs and LXRs, using synthetic ligands improves metabolic homeostasis. Nuclear receptors modulate gene expression through recruitment of large protein complexes, which modify the structure of chromatin through histone modification (Fig. 3). Unliganded receptors interact with co-repressors, most notably silencing mediator of retinoic and thyroid hormone receptors (SMRT) and nuclear receptor co-repressor (NCoR), which recruit histone deacetylases (HDACs), particularly HDAC3, to deacetylate histones leading to a tighter chromatin structure and less accessible promoters. Co-activators such as PPARγ co-activator-1α (PGC-1α) and steroid receptor co-activators (SRC1/2/3) and histone acetylases (p300/CBP) are recruited to ligand-bound nuclear receptors to upregulate gene expression. Ligand-dependent repression of inflammatory gene expression by nuclear receptors is less understood and is mediated by several unconventional mechanisms (described below).

**Nuclear Receptors and Adipocyte Function**

The PPARs (PPARα, β/δ and γ) are activated by dietary fatty acids and have been shown to modulate various cellular functions, mostly related to fat transport, storage and oxidation. PPARγ in particular has been well studied in its regulation of adipose tissue. The mammalian PPARγ was cloned by analysis of the adipose-specific enhancer from the adipocyte protein 2 (ap2) gene, an adipocyte-specific fatty-acid binding protein. It later became clear that PPARγ is needed for adipocyte differentiation and maintenance in vivo and that anti-diabetic drugs, thiazolidinediones (TZDs), were synthetic ligands for PPARγ. It is thought that TZDs improve insulin sensitivity partly through promoting fatty acid storage as triglycerides in adipocytes, thereby reducing lipotoxicity. PPARδ, on the other hand, is a regulator of fat burning. Treatment of db/db mice with a PPARδ agonist improves insulin sensitivity, while PPARδ-deficient mice show reduced energy expenditure. PPARδ is also involved in brown adipose tissue (BAT) metabolism. Unlike WAT that stores excess energy in the form of triacylglycerol, BAT dissipates energy as heat. In BAT, PPARδ regulates mitochondrial oxidative metabolism and thermogenesis through PGC-1α. PGC-1α is a cold-inducible, master regulator of mitochondrial biogenesis. The SRC co-activators also play a role in adipocyte differentiation and BAT thermogenesis. The role of co-repressors in PPAR-mediated lipid metabolism is more complex. Disruption of SMRT-PPARγ interaction leads to spontaneous differentiation of pre-adipocytes to adipocytes. Increased SMRT-PPARγ interaction in vivo causes obesity, premature aging and related metabolic diseases due to suppressed fatty acid oxidation and mitochondrial oxidative metabolism. Finally, recent work has identified NCoR as a negative regulator of adipogenesis both in vivo and in vitro.
Nuclear Receptors and Macrophage Activation

The notion that PPARγ is critical for adipocyte differentiation prompted investigation of similar functions in other cell types. Early studies showed that PPARγ was involved in a signaling pathway controlling differentiation in monocytic cells, although later work using genetic models of PPARγ−/− mice showed that macrophage differentiation was not critically dependent on PPARγ. These studies initiated a new field of research examining the regulatory effects of nuclear receptors on inflammation. We now know that in addition to the well-characterized immuno-suppressive activity of glucocorticoid receptor, activation of several nuclear receptors, particularly PPARs and LXRs, are able to modulate macrophage activation through several anti-inflammatory mechanisms or by Th2 polarization.

Anti-inflammatory mechanisms. Previous work examining anti-inflammatory effects of PPARs was conducted mainly in the macrophage in the context of vascular inflammation and atherosclerosis. However, PPARs are expressed in several cell types in the vasculature (e.g., immune cells, endothelial cells and smooth muscle cells) and have been shown to inhibit the production of several inflammatory mediators and cytokines in these cells. For example, treatment with PPARγ agonist fenofibrate in patients with hyperlipidemia and atherosclerosis decreases circulating levels of fibrinogen, IL-6, CRP, IFN-γ and TNF-α. In aortic smooth muscle cells, PPARγ inhibits the expression of classical mediators of inflammation such as IL-6 and cyclooxygenase-2 via repression of NFκB signaling. PPARγ activation inhibits the expression of iNOS, gelatinase B and scavenger receptor A in response to the prostaglandin D2 metabolite, 15-deoxy-prostaglandin J2 (15dPGJ2), and synthetic PPARγ ligands. PPARγ expression was shown to be induced by IL-4 in macrophages and was later demonstrated to have a crucial role in macrophage M2 polarization (discussed below). It was proposed that PPARγ inhibited inflammation by antagonist actions on the activities of inflammatory transcription factors, including activator protein 1 (AP-1), NFκB and signal transducer and activator of transcription 1 (STAT1). However, several synthetic and natural PPARγ agonists at higher concentrations produce anti-inflammatory responses through PPARγ-independent mechanisms, such as the direct inhibition and modification of IKK-β. The Glass laboratory identified a transrepression...
mechanism whereby liganded nuclear receptors actually repress transcription of inflammatory genes through post-translational modifications and protein-protein interactions. In this model, ligand-bound PPARγ is SUMOylated, which in turn recruits NCoR co-repressor complexes to directly repress NFκB target genes (Fig. 3). Similar mechanisms were subsequently identified for glucocorticoid receptor and LXR. Compared with the other PPARs, less is known about the roles of PPARδ in inflammation. PPARδ agonists also inhibit LPS-inducible genes. Lee et al. proposed a unique transcriptional pathway through which PPARδ exerts its anti-inflammatory effects by sequestering the transcriptional repressor BCL-6 away from the promoters of inflammatory genes, such as MCP-1, IL-1β and MMP-9. BCL-6 is released from ligand-activated PPARδ and becomes available to inhibit inflammatory gene expression (Fig. 3).

**Th2 polarization.** Th2 cytokines, particularly IL-4 and IL-13, mediate M2 activation. The observation that both PPARγ and PPARδ levels in macrophages are increased by IL-4/IL-13 initiated closer examination of the role of macrophage PPARs in mouse models of diet-induced obesity. In the macrophage, IL-4/IL-13-induced alternative activation is associated with increased fatty acid β-oxidation and oxidative metabolism, programs that are transcriptionally controlled by the PPARs and PPARδ. Accordingly, PPARδ and PPARγ were shown to regulate the expression of certain M2 genes and control alternative activation in the macrophage. Mice with myeloid specific deletion of PPARα or PPARδ show increased M1 and decreased M2 markers in WAT and liver. Of note, in a separate study, mice lacking PPARα or PPARδ in hematopoietic cells did not show expected metabolic phenotypes. Interestingly, STAT6, a Th2 transcription factor, was shown to facilitate the PPARγ response to IL-4 at the transcriptional level in macrophages, with the net effect being an increase in the number of regulated genes and in the magnitude of responses.

**Nuclear Receptors in Paracrine Interaction of Adipose Tissue Resident Macrophages with Adipocytes**

Given their important functions in adipocytes and macrophages, activation of PPARs is expected to improve WAT homeostasis and reduce metabolic inflammation. In adipocytes, PPARγ and PPARα reduce fatty acid efflux by promoting fat storage or burning, respectively (Fig. 4). In macrophages, PPARs can suppress inflammatory responses by anti-inflammatory mechanisms or by Th2 polarization. In fact, myeloid-specific PPAR deletion experiments described above are consistent with the notion that the beneficial activities of PPARs may rely in part on their anti-inflammatory properties. PPARγ deletion in macrophages is associated with impaired glucose tolerance and insulin resistance in response to a high fat diet. Additionally, it has been demonstrated that the insulin sensitizing effect of rosiglitazone was decreased when PPARγ was inactivated in macrophages.

Kang et al. proposed a paracrine pathway in which adipose tissue-derived IL-13 activates macrophage PPARδ to modulate M2 activation (Fig. 4). Disruption of this pathway by myeloid-specific PPARδ gene deletion leads to WAT inflammation, hepatosteatosis and systemic insulin resistance. Collectively, these studies support the notion that the dynamics between adipocytes and ATMs play a key role in the initiation of chronic inflammation and demonstrate that the PPAR signaling pathway serves as an important regulatory node in the control of lipid-induced metabolic stress and “para-inflammation.”

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**Figure 4.** Role of PPARs in the paracrine interaction between adipocytes and adipose tissue macrophages. As sensors of dietary fatty acids, PPARs play an important role in maintenance of white adipose tissue homeostasis. In adipocytes, PPARγ activation reduces fatty acid efflux by promoting fat storage and increasing adiponectin production, which improves systemic lipid and glucose metabolism. In the macrophage, PPARs can suppress inflammatory responses by anti-inflammatory mechanisms or by Th2 polarization, which increases the production of an anti-inflammatory cytokine, IL-10. Th2 cytokines are produced locally by many cell types (eosinophils, T lymphocytes, mast cells and adipocytes) to activate downstream transcription factors in the macrophage, including STAT6 and PPARδ/PPARγ. Studies have demonstrated that disruption of the IL-13-PPARδ paracrine pathway leads to white adipose tissue inflammation and insulin resistance, highlighting the importance of PPAR signaling in controlling the initiation of metabolic inflammation.
Conclusion

At the signaling level, inflammatory and metabolic processes are integral and linked to components of metabolic diseases. Modulation of the activities of nuclear receptors is a potential therapeutic strategy to restore the imbalance of pro-inflammatory and anti-inflammatory signaling for preventing and/or treating obesity-related metabolic and cardiovascular diseases that are thought to be triggered by unresolved, chronic inflammation. In fact, PPAR agonists are currently used to treat type 2 diabetes and dyslipidemia. However, the side effects of PPAR\textsuperscript{\textregistered} ligands in cardiovascular complications have limited their use. Future studies aiming to isolate localized effects of PPARs within the WAT microenvironment, either through targeting tissue-specific co-activators or repressors or identifying selective synthetic modulators, will provide new therapeutic opportunities. New mechanistic insights derived from these studies will also help define relative contributions from PPAR signaling in adipocytes or immune cells in the control of metabolic inflammation and associated diseases.

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