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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; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; FFA, free fatty acids; FXR, farnesoid X receptor; HDAC, histone deacetylase; LPS, lipopolysaccharide; LXR, liver X receptor; MCP-1, monocyte chemotactic protein-1; NCoR, nuclear receptor co-repressor; NFκB, nuclear factor kappa B; PGC, PPAR γ co-activator; PPAR, peroxisome proliferator-activated receptor; ROR, retinoid-related orphan receptor; SMRT, silencing mediator for retinoic acid and thyroid hormone receptors; SRC, steroid receptor co-activator; STAT, signal transducer and activators of transcription; TGF-β1, tumor growth factor β1; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; WAT, white adipose tissue

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 ATM 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 1994[1] 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 endocrine[3] 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-inflammation[6] and is dependent on white adipose tissue (WAT) infiltration by macrophages.[7-9] 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.[10-14]

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,

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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),[10] interleukin 6 (IL-6),[15] inducible nitric oxide synthase (iNOS),[16] tumor growth factor β1 (TGF-β1),[17] and monocyte chemotactic protein-1 (MCP-1).[11] In addition to adipocytes, the stromal-vascular fraction of WAT contains a heterogenic 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.[8,9] 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.[8,9] 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.[8] Follow-up studies demonstrated that human visceral WAT, the accumulation of which is associated with alteration in lipid profile and insulin sensitivity,[18-23] also contains macrophages in greater number in obesity.[12] In paired biopsies obtained from obese adults during bariatric surgery, there were twice as many macrophages in visceral as in subcutaneous WAT.[24] Similar to the results derived from mouse models, studies of human WAT showed that non-adipocyte cells were the main sources of inflammatory cytokines.[7,12] Analysis of adipose tissue in obesity shows the convergence of macrophages on adipocytes of necrotic appearance, described as "crown-like structures."[25] 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.[13] 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/macrophage interactions. Data exists showing a positive correlation between macrophage infiltration of visceral fat and the severity of hepatic damage in obese patients.[24] 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 *fa/fa* rats caused an increase in peripheral glucose uptake in response to insulin.[10] 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.[14] Inflammatory signaling pathways, including that of TNFα, are mediated by several protein kinases, such as IκB kinase (IKKs) and c-Jun N-terminal kinases (JNKs). Mice lacking *Ikk-β*, a regulator of inflammatory responses through activation of NFκB (nuclear factor kappa B), in myeloid cells are protected from insulin resistance.[28] 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.[29] *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

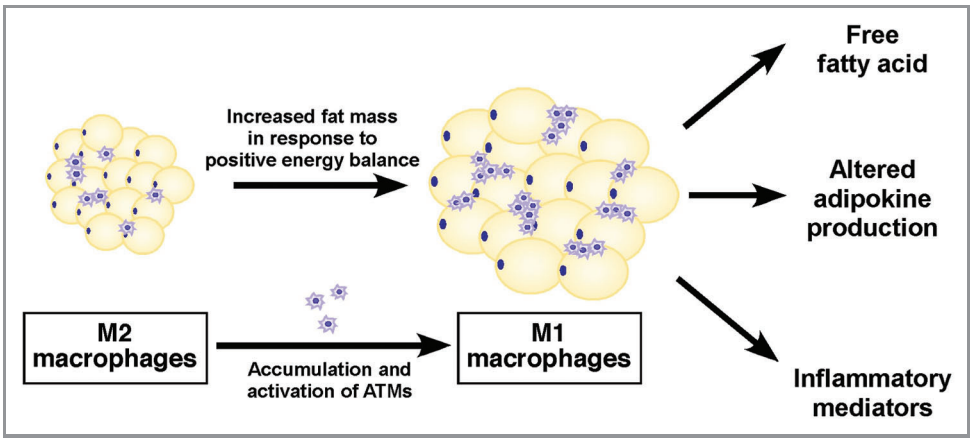

Figure 1. White adipose tissue and the metabolic complications of obesity. In addition to its function in energy storage, adipose tissue is now considered an endocrine organ, producing circulating molecules, including adipokines (e.g., leptin and adiponectin), inflammatory mediators (e.g., TNF-α, IL-6, IL-1β and MCP-1) and bioactive lipids (e.g., FFA) that have important impacts on metabolic homeostasis. The maladaptation of adipocytes in response to chronic positive energy balance leads to increased production of pro-inflammatory chemokines/cytokines and release of non-esterified FFA, resulting in the infiltration of pro-inflammatory macrophages (M1) and a shift in the balance between pro- and anti-inflammatory (M2) macrophage populations within white adipose tissues. This so called "para-inflammation" or metabolic inflammation is associated with obesity-related metabolic syndrome.

hematopoietic cells has no effect on adiposity but confers protection against high fat diet-induced inflammation and insulin resistance.[30] However, this latter result was not reproducible in a separate study.[31] Lastly, MCP-1, a chemokine that recruits macrophages, and its receptor CCR2, have been shown to promote insulin resistance.[11,32] Interestingly, addition of MCP-1 to mature adipocytes in vitro decreased insulin-stimulated glucose uptake and the expression of several adipogenic genes, suggesting that chemokines may have a direct impact on metabolic homeostasis, in addition to their role in mediating immune cell infiltration.[11]

Loss of alternatively activated macrophages facilitates insulin resistance. Using mouse models in which macrophage alternative activation (M2) was genetically impaired, susceptibility to diet-induced obesity, hepatic steatosis, insulin resistance and glucose intolerance all increased.[33,34] We will discuss these studies in greater details below.

Macrophage insulin signaling in inflammation and metabolic diseases. Insulin signaling is thought to affect macrophage function. However, mechanistic insights in this area are lacking. Studies have shown that deletion of the gene *Sorb1* encoding Cbl-associated protein (Cap), a molecule implicated in insulin-stimulated glucose uptake, protects against high fat diet-induced insulin resistance and reduces inflammation. The insulin sensitivity phenotype could be transferred to wild-type mice on high fat diet by transplantation of *Sorb1*$^{-/-}$ bone marrow,[35] supporting a role for macrophage insulin signaling in modulation of systemic insulin sensitivity. Studies in atherosclerosis with insulin receptor knock out macrophages show conflicting results. In the background of LDL receptor knockout mice, these macrophages show an impaired ability to handle ER stress-induced apoptosis leading to worsening of atherosclerotic plaques.[36] In contrast, insulin receptor and apoE double knockout macrophages were associated with less inflammation and smaller atherosclerotic lesions.[37]

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.[38] 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.[40] While it is known that visceral WAT has higher levels of lipolysis and contains more ATMs than abdominal subcutaneous WAT,[41-43] recent studies have characterized the effects of weight loss and fasting on ATMs in mice and identified a role for lipolysis in macrophage recruitment.[44] 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

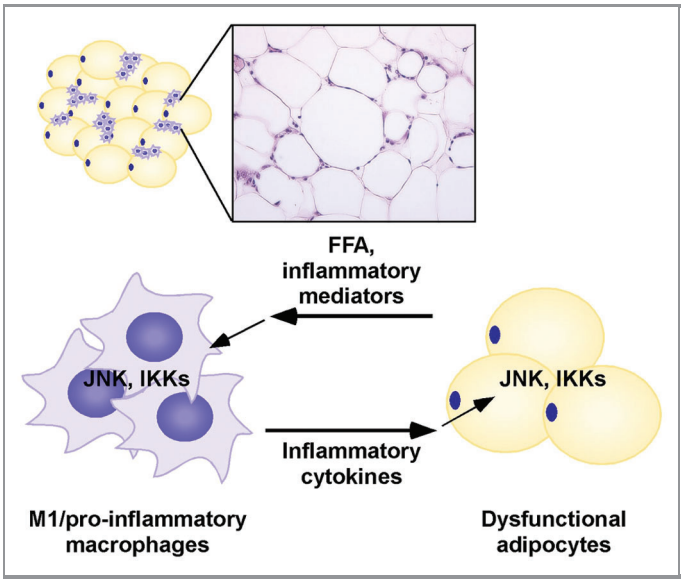

Figure 2. Adipose tissue macrophages and the origin of metabolic inflammation. In obesity, adipose tissue resident macrophages exhibit an M1/pro-inflammatory phenotype. They are activated either by systemic chronic inflammation before entering adipose tissues or by locally produced inflammatory mediators. Histologically, they are seen to be concentrated around dying fat cells (insert, top panel). These M1 macrophages produce pro-inflammatory cytokines (e.g., TNF-α and IL-1β) known to induce metabolic dysfunction and insulin resistance in neighboring adipocytes through inflammatory signaling kinases (e.g., JNK and IKKs), creating an unresolvable inflammatory response.

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.[45] 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.[46] 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.[46] 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.[47] 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.[48,49] Co-activators such as PPARγ coactivator-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.[50-52] 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.[53] It later became clear that PPARγ is needed for adipocyte differentiation and maintenance in vivo[54-58] and that anti-diabetic drugs, thiazolidinediones (TZDs), were synthetic ligands for PPARγ.[59,60] 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.[61] In genetically predisposed mouse models of obesity (*db/db*), overexpression of constitutively active PPARδ in adipocytes induces expression of genes involved in fatty acid oxidation and energy dissipation, which leads to reduced adiposity and improved lipid profiles.[62] Treatment of *db/db* mice with a PPARδ agonist improves insulin sensitivity, while PPARδ-deficient mice show reduced energy expenditure.[63] 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.[64] PGC-1α is a cold-inducible, master regulator of mitochondrial biogenesis.[65,66] The SRC co-activators also play a role in adipocyte differentiation and BAT thermogenesis.[65,67-69] 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.[70] Increased SMRT-PPAR interaction in vivo causes obesity, premature aging and related metabolic diseases due to suppressed fatty acid oxidation and mitochondrial oxidative metabolism.[71,72] Finally, recent work has identified NCoR as a negative regulator of adipogenesis both in vivo[73] and in vitro.[74]

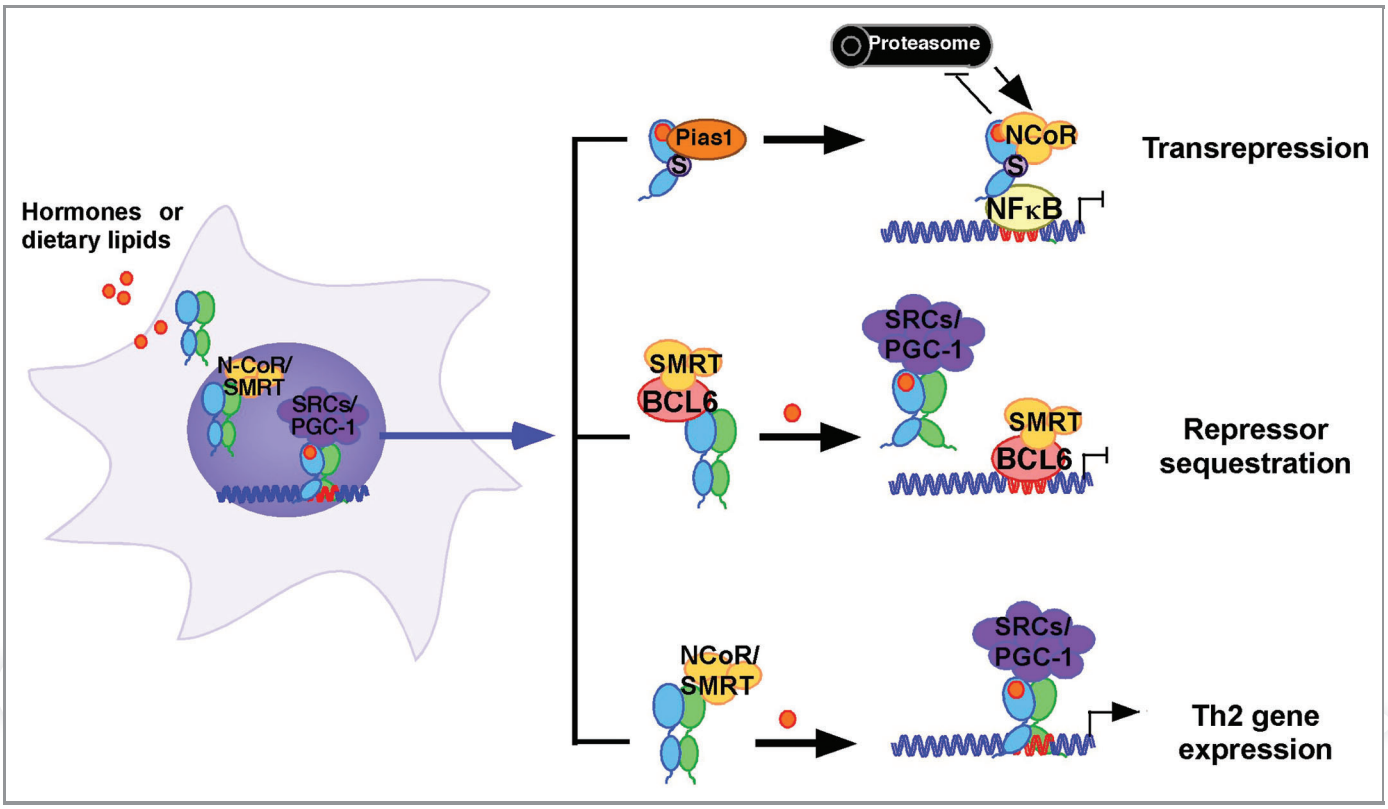

Figure 3. Mechanisms of nuclear receptor action in the macrophage. Nuclear receptors, in the form of homo- or heterodimers, regulate transcription through differential recruitment of co-repressors (e.g., SMRT and NCoR) and co-activators (e.g., SRCs and PGC-1s). In the absence of ligand, nuclear receptors recruit co-repressor complexes to actively repress transcription. Upon ligand binding, the conformation of the receptor changes, releasing the co-repressor complex and recruiting co-activator complexes to activate transcription of target genes. There are at least three different mechanisms by which nuclear receptors regulate target gene expression. The ligand-dependent inhibition of inflammatory gene expression involves unconventional mechanisms (right). In the transrepression model, the liganded nuclear receptor is SUMOylated by SUMO ligase Pias1, which is then recruited to promoters of NFκB target genes to block degradation of co-repressor complexes. In the repressor sequestration model, unliganded-PPARδ/SMRT sequesters the repressor BCL-6 by direct interaction. Upon ligand binding, BCL-6/SMRT dissociates from PPARδ to repress pro-inflammatory target genes. Liganded PPARδ also controls the expression of M2 genes, thereby promoting macrophage alternative activation.

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,[75,76] although later work using genetic models of *PPARγ*$^{-/-}$ mice showed that macrophage differentiation was not critically dependent on PPARγ.[77,78] 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 PPARα agonist fenofibrate in patients with hyperlipidemia and atherosclerosis decreases circulating levels of fibrinogen, IL-6, CRP, IFN-γ and TNF-α.[79,80] In aortic smooth muscle cells, PPARα inhibits the expression of classical mediators of inflammation such as IL-6 and cyclooxygenase-2 via repression of NFκB signaling.[79] 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.[81] PPARγ expression was shown to be induced by IL-4 in macrophages[82] 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.[83] 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.[84] In this model, ligand-bound PPARγ is SUMOylated, which in turn recruits NCoR co-repressor complexes to directly repress NFκB target genes (**Fig. 3**).[85] Similar mechanisms were subsequently identified for glucocorticoid receptor[86] and LXR.[87,88] Compared with the other PPARs, less is known about the roles of PPARδ in inflammation. PPARδ agonists also inhibit LPS-inducible genes.[89] 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.[90] BCL-6 is released from ligand-activated PPARδ and becomes available to inhibit inflammatory gene expression (**Fig. 3**).[91]

Th2 polarization. Th2 cytokines, particularly IL-4 and IL-13, mediate M2 activation.[26] 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.[33,34,92-95] 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 PPARγ and PPARδ.[33,34,94,96,97] Accordingly, PPARδ and PPARγ were shown to regulate the expression of certain M2 genes and control alternative activation in the macrophage.[33,34,93] Mice with myeloid specific deletion of PPARδ or PPARγ show increased M1 and decreased M2 markers in WAT and liver.[33,34,92,93,98] Of note, in a separate study, mice lacking PPARγ or PPARδ in hematopoietic cells did not show expected metabolic phenotypes.[99] 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.[100]

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 PPARδ 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.[33] Additionally, it has been demonstrated that the insulin sensitizing effect of rosiglitazone was decreased when PPARγ was inactivated in macrophages.[92] Kang et al. proposed a paracrine pathway in which adipose tissue-derived IL-13 activates macrophage PPARδ to modulate M2 activation (**Fig. 4**).[34] 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."

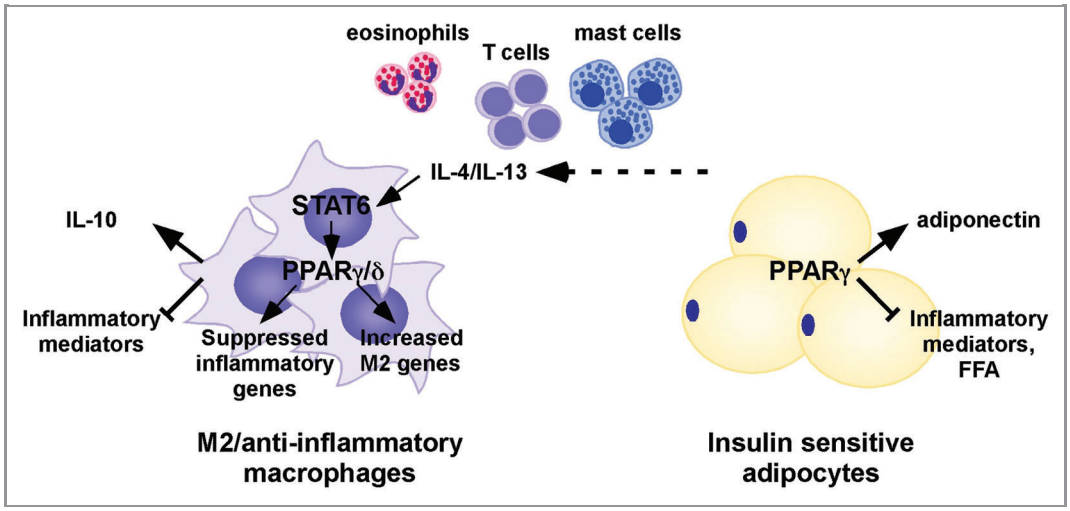

Figure 4. Role of PPARs in the paracrine interaction between adipocytes and adipose tissue macrophages. As sensors of dietary fatty acids, PPARs play an important role in maintenance of white adipose tissue homeostasis. In adipocytes, PPARγ activation reduces fatty acid efflux by promoting fat storage 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 PPARγ 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/co-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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References

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-32; PMID:7984236; http://dx.doi.org/10.1038/372425a0
2. Shuldiner AR, Yang R, Gong DW. Resistin, obesity and insulin resistance–the emerging role of the adipocyte as an endocrine organ. N Engl J Med 2001; 345:1345-6; PMID:11794158; http://dx.doi.org/10.1056/NEJM200111013451814
3. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004; 92:347-55; PMID:15469638; http://dx.doi.org/10.1079/BJN20041213
4. Karastergiou K, Mohamed-Ali V. The autocrine and paracrine roles of adipokines. Mol Cell Endocrinol 2010; 318:69-78; PMID:19948207; http://dx.doi.org/10.1016/j.mce.2009.11.011
5. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860-7; PMID:17167474; http://dx.doi.org/10.1038/nature05485
6. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454:428-35; PMID:18650913; http://dx.doi.org/10.1038/nature07201
7. Fain JN, Bahouth SW, Madan AK. TNFalpha release by the nonfat cells of human adipose tissue. Int J Obes Relat Metab Disord 2004; 28:616-22; PMID:14770194; http://dx.doi.org/10.1038/sj.ijo.0802594
8. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112:1796-808; PMID:14679176
9. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112:1821-30; PMID:14679177
10. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993; 259:87-91; PMID:7678183; http://dx.doi.org/10.1126/science.7678183
11. Sartipy P, Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. Proc Natl Acad Sci USA 2003; 100:7265-70; PMID:12756299; http://dx.doi.org/10.1073/pnas.1133870100
12. Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, et al. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 2006; 49:744-7; PMID:16496121; http://dx.doi.org/10.1007/s00125-006-0173-z
13. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; 117:175-84; PMID:17200717; http://dx.doi.org/10.1172/JCI29881
14. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 1997; 389:610-4; PMID:9335502; http://dx.doi.org/10.1038/39335
15. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998; 83: 847-50; PMID:9506738; http://dx.doi.org/10.1210/jc.83.3.847
16. Perreault M, Marette A. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. Nat Med 2001; 7:1138-43; PMID:11590438; http://dx.doi.org/10.1038/nm1001-1138
17. Samad F, Yamamoto K, Pandey M, Loskutoff DJ. Elevated expression of transforming growth factor-beta in adipose tissue from obese mice. Mol Med 1997; 3:37-48; PMID:9132278
18. Couillard C, Bergeron N, Prud'homme D, Bergeron J, Tremblay A, Bouchard C, et al. Postprandial triglyceride response in visceral obesity in men. Diabetes 1998; 47:953-60; PMID:9604874; http://dx.doi.org/10.2337/diabetes.47.6.953
19. Després JP, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien PJ, et al. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. Diabetes 1989; 38:304-9; PMID:2645187; http://dx.doi.org/10.2337/diabetes.38.3.304
20. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987; 36:54-9; PMID:3796297; http://dx.doi.org/10.1016/0026-0495(87)90063-1
21. Peiris AN, Sothmann MS, Hoffmann RG, Hennes MI, Wilson CR, Gustafson AB, et al. Adiposity, fat distribution, and cardiovascular risk. Ann Intern Med 1989; 110:867-72; PMID:2655520
22. Pouliot MC, Despres JP, Nadeau A, Moorjani S. Prud'Homme D, Lupien PJ, Tremblay A, Bouchard C. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 1992; 41:826-34; PMID:1612197; http://dx.doi.org/10.2337/diabetes.41.7.826
23. Tchernof A, Lamarche B. Prud'Homme D, Nadeau A, Moorjani S, Labrie F, Lupien PJ, Despres JP. The dense LDL phenotype. Association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. Diabetes Care 1996; 19:629-37; PMID:8725863; http://dx.doi.org/10.2337/diacare.19.6.629
24. Cancello R, Tordjman J, Poitou C, Guilhem G, Bouillot JL, Hugol D, et al. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. Diabetes 2006; 55:1554-61; PMID:16731817; http://dx.doi.org/10.2337/db06-0133
25. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 2005; 46:2347-55; PMID:16150820; http://dx.doi.org/10.1194/jlr.M500294-JLR200
26. Gordon S. Alternative activation of macrophages. Nat Rev Immunol 2003; 3:23-35; PMID:12511873; http://dx.doi.org/10.1038/nri978
27. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 2004; 25:677-86; PMID:15530839; http://dx.doi.org/10.1016/j.it.2004.09.015
28. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 2005; 11:191-8; PMID:15685170; http://dx.doi.org/10.1038/nm1185
29. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature 2002; 420:333-6; PMID:12447443; http://dx.doi.org/10.1038/nature01137
30. Solinas G, Vilcu C, Neels JG, Bandyopadhyay GK, Luo JL, Naugler W, et al. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab 2007; 6:386-97; PMID:17983584; http://dx.doi.org/10.1016/j.cmet.2007.09.011
31. Vallerie SN, Furuhashi M, Fucho R, Hotamisligil GS. A predominant role for parenchymal c-Jun amino terminal kinase (JNK) in the regulation of systemic insulin sensitivity. PLoS ONE 2008; 3:e3151; PMID:18773087; http://dx.doi.org/10.1371/journal.pone.0003151
32. Weisberg SP, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, et al. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. J Clin Invest 2006; 116:115-24; PMID:16341265; http://dx.doi.org/10.1172/JCI24335
33. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, et al. Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. Nature 2007; 447:1116-20; PMID:17515919; http://dx.doi.org/10.1038/nature05894

34. Kang K, Reilly SM, Karabacak V, Gangl MR, Fitzgerald K, Hatano B, et al. Adipocyte-derived Th2 cytokines and myeloid PPARdelta regulate macrophage polarization and insulin sensitivity. Cell Metab 2008; 7:485-95; PMID:18522830; http://dx.doi.org/10.1016/j.cmet.2008.04.002
35. Lesniewski LA, Hosch SE, Neels JG, de Luca C, Pashmforoush M, Lumeng CN, et al. Bone marrow-specific Cap gene deletion protects against high-fat diet-induced insulin resistance. Nat Med 2007; 13:455-62; PMID:17351624; http://dx.doi.org/10.1038/nm1550
36. Han S, Liang CP, DeVries-Seimon T, Ranalletta M, Welch CL, Collins-Fletcher K, et al. Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions. Cell Metab 2006; 3:257-66; PMID:16581003; http://dx.doi.org/10.1016/j.cmet.2006.02.008
37. Baumgartl J, Baudler S, Scherner M, Babaev V, Makowski L, Suttles J, et al. Myeloid lineage cell-restricted insulin resistance protects apolipoproteinE-deficient mice against atherosclerosis. Cell Metab 2006; 3:247-56; PMID:16581002; http://dx.doi.org/10.1016/j.cmet.2006.02.010
38. Kabir M, Catalano KJ, Ananthnarayan S, Kim SP, Van Citters GW, Dea MK, et al. Molecular evidence supporting the portal theory: a causative link between visceral adiposity and hepatic insulin resistance. Am J Physiol Endocrinol Metab 2005; 288:E454-61; PMID:15522994; http://dx.doi.org/10.1152/ajpendo.00203.2004
39. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol 2003; 14:281-7; PMID:12840659; http://dx.doi.org/10.1097/00041433-200306000-00008
40. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006; 116:3015-25; PMID:17053832; http://dx.doi.org/10.1172/JCI28898
41. Curat CA, Miranville A, Sengenes C, Diehl M, Tonus C, Busse R, et al. From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. Diabetes 2004; 53:1285-92; PMID:15111498; http://dx.doi.org/10.2337/diabetes.53.5.1285
42. Mårin P, Andersson B, Ottosson M, Olbe L, Chowdhury B, Kvist H, et al. The morphology and metabolism of intraabdominal adipose tissue in men. Metabolism 1992; 41:1242-8; PMID:1435298; http://dx.doi.org/10.1016/0026-0495(92)90016-4
43. Hoffstedt J, Arner P, Hellers G, Lonnqvist F. Variation in adrenergic regulation of lipolysis between omental and subcutaneous adipocytes from obese and non-obese men. J Lipid Res 1997; 38:795-804; PMID:9144094
44. Kosteli A, Sugaru E, Haemmerle G, Martin JF, Lei J, Zechner R, et al. Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. J Clin Invest 2010; 120:3466-79; PMID:20877011; http://dx.doi.org/10.1172/JCI42845
45. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. Science 2001; 294:1866-70; PMID:11729302; http://dx.doi.org/10.1126/science.294.5548.1866
46. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, et al. The nuclear receptor superfamily: the second decade. Cell 1995; 83:835-9; PMID:8521507; http://dx.doi.org/10.1016/0092-8674(95)90199-X
47. Hong C, Tontonoz P. Coordination of inflammation and metabolism by PPAR and LXR nuclear receptors. Curr Opin Genet Dev 2008; 18:461-7; PMID:18782619; http://dx.doi.org/10.1016/j.gde.2008.07.016
48. Privalsky ML. The role of corepressors in transcriptional regulation by nuclear hormone receptors. Annu Rev Physiol 2004; 66:315-60; PMID:14977406; http://dx.doi.org/10.1146/annurev.physiol.66.032802.155556
49. Stanya KJ, Kao HY. New insights into the functions and regulation of the transcriptional corepressors SMRT and N-CoR. Cell Div 2009; 4:7; PMID:19383165; http://dx.doi.org/10.1186/1747-1028-4-7
50. Chen W, Roeder RG. Mediator-dependent nuclear receptor function. Semin Cell Dev Biol 2011; 22:749-58; PMID:21854863; http://dx.doi.org/10.1016/j.semcdb.2011.07.026
51. York B, O'Malley BW. Steroid receptor coactivator (SRC) family: masters of systems biology. J Biol Chem 2010; 285:38743-50; PMID:20956538; http://dx.doi.org/10.1074/jbc.R110.193367
52. Lin JD. Minireview: the PGC-1 coactivator networks: chromatin-remodeling and mitochondrial energy metabolism. Mol Endocrinol 2009; 23:2-10; PMID:19008463; http://dx.doi.org/10.1210/me.2008-0344
53. Graves RA, Tontonoz P, Spiegelman BM. Analysis of a tissue-specific enhancer: ARF6 regulates adipogenic gene expression. Mol Cell Biol 1992; 12:1202-8; PMID:1545801
54. Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, et al. PPAR gamma is required for placental, cardiac, and adipose tissue development. Mol Cell 1999; 4:585-95; PMID:10549290; http://dx.doi.org/10.1016/S1097-2765(00)80209-9
55. He W, Barak Y, Hevener A, Olson P, Liao D, Le J, et al. Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. Proc Natl Acad Sci USA 2003; 100:15712-7; PMID:14660788; http://dx.doi.org/10.1073/pnas.2536828100
56. Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, Komeda K, et al. PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. Mol Cell 1999; 4:597-609; PMID:10549291; http://dx.doi.org/10.1016/S1097-2765(00)80210-5
57. Rosen ED, Sarraf P, Troy AE, Bradwin G, Moore K, Milstone DS, et al. PPAR gamma is required for the differentiation of adipose tissue in vivo and in vitro. Mol Cell 1999; 4:611-7; PMID:10549292; http://dx.doi.org/10.1016/S1097-2765(00)80211-7
58. Tamori Y, Masugi J, Nishino N, Kasuga M. Role of peroxisome proliferator-activated receptor-gamma in maintenance of the characteristics of mature 3T3-L1 adipocytes. Diabetes 2002; 51:2045-55; PMID:12086932; http://dx.doi.org/10.2337/diabetes.51.7.2045
59. Harris PK, Kletzien RF. Localization of a pioglitazone response element in the adipocyte fatty acid-binding protein gene. Mol Pharmacol 1994; 45:439-45; PMID:8145730
60. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell 1995; 83:803-12; PMID:8521497; http://dx.doi.org/10.1016/0092-8674(95)90193-0
61. Reilly SM, Lee CH. PPAR delta as a therapeutic target in metabolic disease. FEBS Lett 2008; 582:26-31; PMID:18036566; http://dx.doi.org/10.1016/j.febslet.2007.11.040
62. Wang YX, Lee CH, Tiep S, Yu RT, Ham J, Kang H, et al. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. Cell 2003; 113:159-70; PMID:12705865; http://dx.doi.org/10.1016/S0092-8674(03)00269-1
63. Lee CH, Olson P, Hevener A, Mehl I, Chong LW, Olefsky JM, et al. PPARdelta regulates glucose metabolism and insulin sensitivity. Proc Natl Acad Sci USA 2006; 103:3444-9; PMID:16492734; http://dx.doi.org/10.1073/pnas.0511253103
64. Pan D, Fujimoto M, Lopes A, Wang YX. Twist-1 is a PPARdelta-inducible, negative-feedback regulator of PGC-1alpha in brown fat metabolism. Cell 2009; 137:73-86; PMID:19345188; http://dx.doi.org/10.1016/j.cell.2009.01.051
65. Louet JF, O'Malley BW. Coregulators in adipogenesis: what could we learn from the SRC (p160) coactivator family? Cell Cycle 2007; 6:2448-52; PMID:17704643; http://dx.doi.org/10.4161/cc.6.20.4777
66. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell 1998; 92:829-39; PMID:9529258; http://dx.doi.org/10.1016/S0092-8674(00)81410-5
67. Louet JF, Coste A, Amazit L, Tannour-Louet M, Wu RC, Tsai SY, et al. Oncogenic steroid receptor coactivator-3 is a key regulator of the white adipogenic program. Proc Natl Acad Sci USA 2006; 103:17868-73; PMID:17098861; http://dx.doi.org/10.1073/pnas.0608711103
68. Picard F, Gehin M, Annicotte J, Rocchi S, Champy MF, O'Malley BW, et al. SRC-1 and TIF2 control energy balance between white and brown adipose tissues. Cell 2002; 111:931-41; PMID:12507421; http://dx.doi.org/10.1016/S0092-8674(02)01169-8
69. Wang Z, Qi C, Krones A, Woodring P, Zhu X, Reddy JK, et al. Critical roles of the p160 transcriptional coactivators p/CIP and SRC-1 in energy balance. Cell Metab 2006; 3:111-22; PMID:16459312; http://dx.doi.org/10.1016/j.cmet.2006.01.002
70. Nofsinger RR, Li P, Hong SH, Jonker JW, Barish GD, Ying H, et al. SMRT repression of nuclear receptors controls the adipogenic set point and metabolic homeostasis. Proc Natl Acad Sci USA 2008; 105:20021-6; PMID:19066220; http://dx.doi.org/10.1073/pnas.0811012105
71. Fang S, Suh JM, Atkins AR, Hong SH, Leblanc M, Nofsinger RR, et al. Corepressor SMRT promotes oxidative phosphorylation in adipose tissue and protects against diet-induced obesity and insulin resistance. Proc Natl Acad Sci USA 2011; 108:3412-7; PMID:21300871; http://dx.doi.org/10.1073/pnas.1017707108
72. Reilly SM, Bhargava P, Liu S, Gangl MR, Gorgun C, Nofsinger RR, et al. Nuclear receptor corepressor SMRT regulates mitochondrial oxidative metabolism and mediates aging-related metabolic deterioration. Cell Metab 2010; 12:643-53; PMID:21109196; http://dx.doi.org/10.1016/j.cmet.2010.11.007
73. Li P, Fan W, Xu J, Lu M, Yamamoto H, Auwerx J, et al. Adipocyte NCoR Knockout Decreases PPAR^3 Phosphorylation and Enhances PPAR^3 Activity and Insulin Sensitivity. Cell 2011; 147:815-26; PMID:22078880; http://dx.doi.org/10.1016/j.cell.2011.09.050
74. Goodson ML, Mengeling BJ, Jonas BA, Privalsky ML. Alternative mRNA splicing of corepressors generates variants that play opposing roles in adipocyte differentiation. J Biol Chem 2011; 286:44988-99; PMID:22065574; http://dx.doi.org/10.1074/jbc.M111.2916.25
75. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell 1998; 93:241-52; PMID:9568716; http://dx.doi.org/10.1016/S0092-8674(00)81575-5
76. Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. Cell 1998; 93:229-40; PMID:9568715; http://dx.doi.org/10.1016/S0092-8674(00)81574-3
77. Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM. PPAR-gamma dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. Nat Med 2001; 7:48-52; PMID:11135615; http://dx.doi.org/10.1038/83336
78. Moore KJ, Rosen ED, Fitzgerald ML, Randow F, Andersson LP, Altshuler D, et al. The role of PPAR-gamma in macrophage differentiation and cholesterol uptake. Nat Med 2001; 7:41-7; PMID:11135614; http://dx.doi.org/10.1038/83328

79. Staels B, Koenig W, Habib A, Merval R, Lebret M, Torra IP, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. Nature 1998; 393:790-3; PMID:9655393; http://dx.doi.org/10.1038/31701
80. Madej A, Okopien B, Kowalski J, Zielinski M, Wysocki J, Szygula B, et al. Effects of fenofibrate on plasma cytokine concentrations in patients with atherosclerosis and hyperlipoproteinemia IIb. Int J Clin Pharmacol Ther 1998; 36:345-9; PMID:9660044
81. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 1998; 391:79-82; PMID:9422508; http://dx.doi.org/10.1038/34178
82. Huang JT, Welch JS, Ricote M, Binder CJ, Willson TM, Kelly C, et al. Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase. Nature 1999; 400:378-82; PMID:10432118; http://dx.doi.org/10.1038/22572
83. Rossi A, Kapahi P, Natoli G, Takahashi T, Chen Y, Karin M, et al. Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IkappaB kinase. Nature 2000; 403:103-8; PMID:10638762; http://dx.doi.org/10.1038/47520
84. Glass CK, Saijo K. Nuclear receptor transrepression pathways that regulate inflammation in macrophages and T cells. Nat Rev Immunol 2010; 10:365-76; PMID:20414208; http://dx.doi.org/10.1038/nri2748
85. Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, et al. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. Nature 2005; 437:759-63; PMID:16127449; http://dx.doi.org/10.1038/nature03988
86. Ogawa S, Lozach J, Benner C, Pascual G, Tangirala RK, Westin S, et al. Molecular determinants of crosstalk between nuclear receptors and toll-like receptors. Cell 2005; 122:707-21; PMID:16143103; http://dx.doi.org/10.1016/j.cell.2005.06.029
87. Ghisletti S, Huang W, Ogawa S, Pascual G, Lin ME, Willson TM, et al. Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression by LXRs and PPARgamma. Mol Cell 2007; 25:57-70; PMID:17218271; http://dx.doi.org/10.1016/j.molcel.2006.11.022
88. Huang W, Ghisletti S, Perissi V, Rosenfeld MG, Glass CK. Transcriptional integration of TLR2 and TLR4 signaling at the NCoR derepression checkpoint. Mol Cell 2009; 35:48-57; PMID:19595715; http://dx.doi.org/10.1016/j.molcel.2009.05.023
89. Welch JS, Ricote M, Akiyama TE, Gonzalez FJ, Glass CK. PPARgamma and PPARdelta negatively regulate specific subsets of lipopolysaccharide and IFN-gamma target genes in macrophages. Proc Natl Acad Sci USA 2003; 100:6712-7; PMID:12740443; http://dx.doi.org/10.1073/pnas.1031789100
90. Lee CH, Chawla A, Urbiztondo N, Liao D, Boisvert WA, Evans RM, et al. Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. Science 2003; 302:453-7; PMID:12970571; http://dx.doi.org/10.1126/science.1087344
91. Barish GD, Yu RT, Karunasiri M, Ocampo CB, Dixon J, Benner C, et al. Bcl-6 and NF-kappaB cistromes mediate opposing regulation of the innate immune response. Genes Dev 2010; 24:2760-5; PMID:21106671; http://dx.doi.org/10.1101/gad.1998010
92. Hevener AL, Olefsky JM, Reichart D, Nguyen MT, Bandyopadyhay G, Leung HY, et al. Macrophage PPAR gamma is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. J Clin Invest 2007; 117:1658-69; PMID:17525798; http://dx.doi.org/10.1172/JCI31561
93. Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. Cell Metab 2008; 7:496-507; PMID:18522831; http://dx.doi.org/10.1016/j.cmet.2008.04.003
94. Barish GD, Atkins AR, Downes M, Olson P, Chong LW, Nelson M, et al. PPARdelta regulates multiple proinflammatory pathways to suppress atherosclerosis. Proc Natl Acad Sci USA 2008; 105:4271-6; PMID:18337509; http://dx.doi.org/10.1073/pnas.0711875105
95. Li AC, Glass CK. PPAR- and LXR-dependent pathways controlling lipid metabolism and the development of atherosclerosis. J Lipid Res 2004; 45:2161-73; PMID:15489539; http://dx.doi.org/10.1194/jlr.R400010-JLR200
96. Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, et al. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. Cell Metab 2006; 4:13-24; PMID:16814729; http://dx.doi.org/10.1016/j.cmet.2006.05.011
97. Lee CH, Kang K, Mehl IR, Nofsinger R, Alaynick WA, Chong LW, et al. Peroxisome proliferator-activated receptor delta promotes very low-density lipoprotein-derived fatty acid catabolism in the macrophage. Proc Natl Acad Sci USA 2006; 103:2434-9; PMID:16467150; http://dx.doi.org/10.1073/pnas.0510815103
98. Bouhlel MA, Derudas B, Rigamonti E, Dievart R, Brozek J, Haulon S, et al. PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. Cell Metab 2007; 6:137-43; PMID:17681149; http://dx.doi.org/10.1016/j.cmet.2007.06.010
99. Marathe C, Bradley MN, Hong C, Chao L, Wilpitz D, Salazar J, et al. Preserved glucose tolerance in high-fat-fed C57BL/6 mice transplanted with PPARgamma−/−, PPARdelta−/−, PPARgamma-delta−/−, or LXRalphabeta−/− bone marrow. J Lipid Res 2009; 50:214-24; PMID:18772483; http://dx.doi.org/10.1194/jlr.M800189-JLR200
100. Szanto A, Balint BL, Nagy ZS, Barta E, Dezso B, Pap A, et al. STAT6 transcription factor is a facilitator of the nuclear receptor PPARgamma-regulated gene expression in macrophages and dendritic cells. Immunity 2010; 33:699-712; PMID:21093321; http://dx.doi.org/10.1016/j.immuni.2010.11.009