Published in final edited form as:

J Investig Med. 2013 August ; 61(6): 937–941. doi:10.231/JIM.0b013e31829ceb39.

Coordinated Regulation of Adipose Tissue Macrophages by Cellular and Nutritional Signals

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Obesity is rapidly becoming a global epidemic.¹ Not only is obesity a major etiologic factor in insulin resistance and type 2 diabetes mellitus (T2DM), it is also a major contributor to the development of cardiovascular disease, stroke and cancer.^{2,3} Multiple studies have established that obesity is associated with a chronic, low-grade inflammatory tissue state, which can lead to decreased insulin sensitivity.⁴ However, recent studies have started to delineate the specific inflammatory pathways affected, and the key role of adipose tissue macrophages (ATMs) in linking nutritional status to insulin resistance. ATMs can comprise up to 40 percent of cells in obese adipose tissue.⁵ Therefore, understanding mechanisms of ATM activation, recruitment, polarization, and release of inflammatory markers will be paramount to understanding the link between obesity and insulin resistance. This review focuses on how cellular and nutritional signals regulate ATMs, and examines evidence regarding the potential role of ATM activation in causing insulin resistance (Figure 1).

Macrophage recruitment to adipose tissue

Macrophage recruitment is one of the first steps in the initiation of insulin resistance. In general, obesity is characterized by an increase in free fatty acids (FFAs). These FFAs and pro-inflammatory stimuli, such as TNF α , cause adipocytes to secrete chemokines through the chemokine receptor type 2/monocyte chemotactic protein-1 (CCR2/MCP-1) system, thereby providing a chemotactic signal to attract monocytes into adipose tissue. Upon infiltration into adipose tissue, these monocytes appear to polarize into different ATM phenotypes, secreting characteristic patterns of cytokines which attract additional monocytes and generate a positive feedback cycle.³

Supporting an important role for the CCR2/MCP-1 system in ATM recruitment, Weisberg et al. reported decreased adipose macrophage content in CCR2 deficient mice,⁶ suggesting that therapeutic approaches aimed at reducing CCR2 could diminish adipose tissue inflammation and enhance insulin sensitivity. However, Gutierrez et al. further elucidated mechanisms whereby systemic and hematopoietic CCR2 deficiencies impact insulin resistance with high fat feeding, by investigating a specific adipose tissue monocytic cell population, CD11B^{lo}F4/80^{lo}. This highly inflammatory myeloid population accumulates in adipose tissue of CCR2^{-/-} mice but not in CCR2^{+/+} mice, raising the concern that CCR2 antagonism therapy could actually exacerbate adipose tissue inflammation.⁷

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Other studies have focused on the role of peroxisome proliferator-activated receptor gamma (PPAR γ), a nuclear receptor necessary for adipocyte differentiation and maintenance of mature adipocytes. Patsouris et al. demonstrated that PPAR γ agonists dramatically inhibit macrophage accumulation in adipose tissue, both in vitro and in mice.⁸ PPAR γ activation increases production of adiponectin, which in turn has anti-inflammatory effects on adipose tissue. Recently, Koppaka et al. published studies in humans showing that pioglitazone, a high-affinity PPAR γ ligand, reduced ATM content by ~69% in subjects with type 2 diabetes after only 21 days of treatment. Preceding this dramatic decrease in ATM content, pioglitazone treatment significantly lowered MCP-1 expression in adipose tissue and CCR2 expression in ATMs after only 10 days of treatment, suggesting that an early decrease in macrophage chemoattractant factors and their receptors led to a subsequent decrease in ATM content at 21 days.⁹ The authors also reported significant improvement in insulin sensitivity after 21 days of pioglitazone therapy, as assessed by hyperinsulinemic-euglycemic clamps. These findings are the first in humans to explore a time course of PPAR γ agonist effects on the relationships among chemoattractant production and response, ATM and other inflammatory cell content, and insulin sensitivity.

Furthermore, studies have shown that toll-like receptor 4 (TLR4), another receptor for FFAs, is important for macrophage accumulation in adipose tissue. Saberi et al. reported that deletion of the TLR-4 gene protects mice from development of insulin resistance secondary to high-fat feeding and obesity, with a concomitant reduction in macrophage infiltration into adipose tissue.¹⁰ However, other studies suggest that a hematopoietic or global TLR4 deficiency does not reliably reduce ATM content in mice.¹¹⁻¹⁴

Recent studies have identified several additional mechanisms of macrophage infiltration.¹⁵ Two studies demonstrated that reduced oxygen delivery from hypertrophic adipocytes induces adipose tissue hypoxia, which causes adipocyte apoptosis, leading to attraction of phagocytic macrophages into adipose tissue.^{16,17} Additionally, leptin has been identified as a potent monocyte/macrophage chemoattractant in vitro,¹⁸ although one recent study reported that hematopoietic leptin receptor deficiency does not impact ATM accumulation or global insulin sensitivity in mice.¹⁹ Finally, chronic lipolysis has also been proposed as an alternate mechanism of macrophage infiltration. Kosteli et al. reported that caloric restriction in mice leads to a transient increase in basal lipolysis and ATM recruitment, whereas longer periods of weight loss are ultimately associated with a reduction in ATM content. These findings suggest that chronic lipolysis, which tends to be increased in obesity, results in elevated FFA concentrations and may lead to ATM accumulation.²⁰ The above studies highlight the variety of factors influencing the complex biology of macrophage infiltration into adipose tissue.

Macrophage polarization/activation

Two main sub-populations of macrophages have been described: the “classically activated” M1 phenotype, which secretes pro-inflammatory cytokines, and the “alternatively activated” M2 phenotype, which secretes anti-inflammatory cytokines.²¹⁻²² After responding to chemoattractant factors and migrating to adipose tissue, ATMs appear to be able to change their phenotype in response to local signals.²² In general, the adipose tissue of obese animals contains predominantly classically activated (M1) ATMs, whereas lean animals have a larger number of alternatively activated (M2) ATMs, suggesting a role for pro-inflammatory cytokines produced by M1 macrophages in the development of insulin resistance.²³⁻²⁵ Several studies have examined the impact of a high-fat diet on macrophage polarization and activation, although it is noteworthy that many investigators consider classically and alternatively activated macrophages to represent a continuous spectrum rather than two discrete phenotypes.²⁶⁻²⁸ Oh et al. studied the mechanisms by which monocytes in obese

mice migrate into adipose tissue and differentiate into pro-inflammatory ATMs, specifically examining whether monocyte polarization to the M1 phenotype in adipose tissue is predetermined or caused by specific cues arising from adipose tissue itself.²⁹ Monocytes from donor mice, both lean and obese, were transferred to obese recipients. Regardless of the donor source, monocytes migrated to adipose tissue and differentiated into pro-inflammatory ATMs. These findings support the hypothesis that ATM migration and accumulation is mediated by chemoattractant factors arising from adipose tissue itself, with evidence of a major role for the CCR2-MCP-1 system described above. Furthermore, Oh et al. reported that 80-90% of newly-recruited ATMs were CD11c⁺ in obese mice, whereas only ~20% were CD11c⁺ in lean mice. CD11c⁺ ATMs are phenotypically pro-inflammatory or M1-like, as opposed to CD11c⁻ ATMs are phenotypically anti-inflammatory or M2-like.²⁴ This suggests that in obesity, circulating CD11c⁻ monocytes migrate to adipose tissue and differentiate predominantly into the M1-like pro-inflammatory CD11c⁺ ATM phenotype. In contrast, in the lean animals the majority of ATMs are CD11c⁻, consistent with the anti-inflammatory M2 phenotype. Interestingly, Oh et al. also reported that adipose tissue of mice with established obesity, in which the ATMs have not been freshly recruited, contains a majority of CD11c⁻ ATMs as well.²⁹ These CD11c⁻ M2-like macrophages proliferate about 2.5-fold faster than CD11c⁺ macrophages. Therefore, the authors suggest that the predominance of CD11c⁻ ATMs in established obesity could arise from rapid proliferation following a minimal recruitment of monocytes or that ATMs do not differentiate from monocytes.²⁹

Despite this propensity for monocytes to polarize into M1-like macrophage phenotypes in new-onset obesity, ATMs are also capable of some degree of phenotypic switching from one state to another. The effect of omega-3 fatty acids (ω -3 FAs) on ATM polarization in mice is to increase M2 ATM markers (such as arginase 1, IL-10, MGL1, Ym-1, Clec7a, and MMR), and to decrease M1 ATM markers (such as IL-6, TNF- α , IL-1 β , MCP-1, iNOS and CD11c).³⁰ This indicates that ω -3 FAs, through the G protein-coupled receptor 120 (GPR120), may be capable of switching M1 ATMs to M2 ATMs. There is also recent literature demonstrating that TLR4 deficiency promotes ATM polarization towards the M2 phenotype in mice, although this occurs without a concomitant improvement in systemic insulin sensitivity.³¹ These data are consistent with the findings described above, indicating that adipose macrophage content, not phenotype, correlates with insulin resistance in humans. Indeed, among human subjects with type 2 diabetes treated with pioglitazone, improved insulin sensitivity correlates temporally with a decrease in ATM content after 21 days of therapy, whereas macrophage phenotypic switching begins to occur earlier in treatment course.⁹

On the other hand, it is well established that increased numbers of pro-inflammatory M1-like macrophages can lead to insulin resistance³². Han et al reported that the c-Jun NH2 terminal kinase 1 (JNK) signal transduction pathway is needed for pro-inflammatory macrophage polarization. In these mice, only the macrophages that did not express JNK were sensitive to insulin.³³ Similarly, Saberi et al demonstrated that deletion of another inflammatory pathway, the inhibitor of I κ B kinase/nuclear factor κ B pathway, reduces obesity-induced insulin resistance in mice.¹⁰

In addition, the PPAR γ pathway plays an active role in macrophage activation and has beneficial effects on inflammatory, adipokine, and lipid profiles.³⁴ PPAR γ is required for maturation of alternatively activated M2 macrophages, and when this pathway is disrupted, mouse models are more likely to develop diet-induced obesity and insulin resistance.³⁵ In humans, pioglitazone increases levels of adiponectin, an adipocyte-specific protein which has both insulin sensitizing and anti-inflammatory effects.^{36,37} Of note, selective activation of PPAR γ in adipocytes, independent of macrophages, improves insulin sensitivity.³⁴

More recently, plasminogen activator inhibitor-1 (PAI-1), a circulating serine protease inhibitor and hemostatic agent, has been identified as an important inflammatory marker.³⁸ Plasma PAI-1 levels vary proportionally to FFA levels in humans, a finding that has been demonstrated both in lean healthy volunteers and obese subjects with type 2 diabetes.^{39,40} Furthermore, Kishore et al. showed in vivo that elevating FFA concentrations in healthy humans stimulated the expression and production of PAI-1 by ATMs, accompanied by higher serum levels of PAI-1 as well as FFA-induced insulin resistance.⁴¹ This study supported the hypothesis that ATMs are primarily responsible for increased production of PAI-1 in response to elevated serum FFA levels, since increased PAI-1 gene expression in ATMs was reported after FFA infusion, whereas circulating monocytes had low PAI gene expression both before and after FFA infusion. In addition, the authors demonstrated in vitro that adipocyte-conditioned medium was needed to stimulate macrophages to produce PAI-1, suggesting that adipose tissue creates a local paracrine environment to promote PAI-1 production by ATMs.⁴¹ Mathew et al. also recently demonstrated in non-diabetic humans that lipid infusion to increase FFA to levels observed in obesity and type 2 diabetes was associated with a significant increase in PAI-1 levels.⁴² Thus, there is evidence in humans that PAI-1 production by ATMs plays a role in development of insulin resistance.

It should also be noted that FFAs themselves have varying effects on inflammation and insulin sensitivity, depending on their specific type. As noted above, ω -3 FAs have an anti-inflammatory effect.⁴³ In vitro and in vivo studies in mice by Oh et al. demonstrated profound ω -3 FA anti-inflammatory effects on ATM phenotype through activation of GPR120, which functions as an ω -3 FA receptor in pro-inflammatory (M1) macrophages and mature adipocytes. GPR120 activation also improved insulin sensitivity, as demonstrated by clamps studies on the animals, as well as lipid profiles. Therefore, FFAs per se play an important role in the complex interplay between inflammation and glucose metabolism.³⁰

Other immune cell populations and their roles in insulin resistance

Macrophage accumulation and activation in adipose tissue have been the focus of intensive study, but other immune cell populations have also received recent attention. Reports of T lymphocyte, natural killer T cell, mast cell, and B lymphocyte infiltration into adipose tissue suggest a potential role for these leukocyte populations in obesity and insulin resistance.⁴⁴ Winer et al. reported that in mice with diet-induced obesity (DIO), CD4⁺ T lymphocytes, which reside in visceral adipose tissue,⁴⁵ control the progression of obesity-associated metabolic abnormalities. Their analysis of human samples supports the same conclusions.⁴⁵ In addition, Feurer et al. reported that CD4⁺ Foxp3⁺ T regulatory (T_{reg}) cells accumulate in the abdominal fat of wild-type mice, but Treg numbers are drastically reduced in this location in models with obesity-associated insulin resistance. Therefore, T_{reg} depletion was associated with insulin resistance in these animal models.⁴⁶

CD1d-restricted invariant natural killer T (iNKT) cells have also been suggested to be mediators between adipocyte dysfunction and insulin resistance. Schipper et al. reported that iNKT cell-deficient mice placed on a low-fat diet developed an insulin-resistant phenotype without overt adipose tissue inflammation. Therefore, these authors suggest that with a low-fat diet, iNKT cells preserve healthy adipose tissue and inhibit insulin resistance.⁴⁷

Furthermore, B cells play a role in the development of insulin resistance. Winer et al. recently reported that B cell accumulation promotes T cell activation and pro-inflammatory cytokine production in the visceral adipose tissue of DIO mice, and specific IgG antibodies produced by B cells are involved in the development of insulin resistance.⁴⁸ Importantly, treatment of these animals with CD20 monoclonal antibodies reversed the pro-inflammatory

cytokine profile in visceral adipose tissue, lending further support to B cell-derived factors promoting insulin resistance. Finally, Liu et al. reported that mast cells accumulate in adipose tissue of obese mice and humans, and contribute to insulin resistance via cytokine production.⁴⁹ In mice, this metabolic profile is amenable to treatment with mast cell stabilizer therapy. Thus, further research will be critical in clarifying the pathways whereby these immune cell populations can be harnessed to combat obesity and insulin resistance with new therapeutic targets.

Future therapeutic approaches and conclusions

While nutritional regulation of ATMs appears to be very complex, this is a very active area of investigation. Although most of the currently proposed therapeutic interventions target single cytokines or receptors, there is increasing interest in understanding more proximal steps in the pathway of insulin resistance.³

More studies, especially in vivo ones, delineate the paramount role of PPAR γ agonists in modulating insulin resistance. This includes observations using a non-thiazolidinedione (TZD) agonist AG035029, which acts even more specifically on adipose tissue PPAR γ than do pioglitazone, rosiglitazone, or troglitazone.³⁴ This study's gain-of-function PPAR γ models showed that potent PPAR γ activation in adipocytes improves whole-body insulin sensitivity to a similar degree as with systemic TZD treatment. This agonist potentially represents a new class of PPAR γ ligands capable of further improving sensitivity to insulin.³⁴

In conclusion, within the realm of ATM recruitment, polarization, and activation, there is already significant progress in elucidating potential directions for therapeutic approaches that deter obesity-induced inflammation and insulin resistance. With all of these rapid advances, it is exciting that this research may hopefully not only lead to better therapies for T2DM, but also provide potential approaches to prevent this growing epidemic.

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Figure 1.

Schematic diagram depicting cells and factors that regulate the activation of adipose tissue macrophages, and promote their secretion of pro-inflammatory cytokines. Arrowheads depict positive regulation (ie: promotion of a pro-inflammatory state), while blunted arrows represent inhibitory regulation.