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Alternative Macrophage Activation and Metabolism

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Abstract

Obesity and its attendant metabolic disorders represent the great public health challenge of our time. Recent evidence suggests that onset of inflammation in metabolic tissues pathogenically links obesity to insulin resistance and type 2 diabetes. In this review, we briefly summarize the extant literature with special attention to the central role of the tissue-associated macrophage in the initiation of metabolic inflammation. We argue that rather than simple inflammatory disease, obesity and metabolic syndrome represent derangements in macrophage activation with concomitant loss of metabolic coordination. As such, the sequelae of obesity are as much products of the loss of positive macrophage influences as the presence of deleterious inflammation. The therapeutic implications of this conclusion are profound because they suggest that pharmacologic targeting of macrophage activation, rather than purely inflammation, might be efficacious in treating this global epidemic.

Keywords

obesity; insulin resistance; inflammation; diabetes; PPAR

INTRODUCTION

Modern humans represent a great survival success story: in an evolutionary blink of an eye, we sprung from a natural state of chronic starvation and activity to one of caloric plenty and leisure. The precipitate rush from savannah to Subway™, however, left little time for our metabolic physiology to catch up; with a physiology shaped by ~200 million years of starving mammals—and ~200,000 years of starving humans—we are ill-adapted to our new-found dietary riches and inactivity. We are, in effect, living a McDonald's™ culture with a Pleistocene metabolism.

The obvious, but no less lamentable, denouement of this mismatch is an epidemic of obesity and its accompanying metabolic disorders. At last count, over one in three adults in the United States was obese and nearly 75% were overweight (1). The mortality burden

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MINI-GLOSSARY

The mini-glossary of key terms is the same as the acronym list.

DISCLOSURE STATEMENT

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associated with these figures is staggering: 300,000 – 400,000 deaths per year in the United States alone are directly attributable to obesity, putting it on par with smoking with regards to its public health impact (2; 3). Indeed, Olshanksy and colleagues predict that the unabated increase in obesity, especially in children, would lead to a plateau or decrease in US life expectancy in the first half of this century (4).

Much of the mortality attributed to obesity is due to the metabolic disorders of insulin resistance, glucose intolerance, dyslipdemia, and hypertension—collectively known as metabolic syndrome—and their well-documented cardiovascular sequelae (5); however, more recent evidence has implicated obesity as a major risk factor in more than a dozen different cancers, hepatic and renal failure, thrombotic disease, and many infectious diseases (6). These findings suggest that obesity's toll on our health, already known to be fearsome, is greatly understated.

Recognition of obesity's catastrophic health sequelae has engendered intense interest regarding its pathophysiology and led to the description of dozens of genes, scores of environmental and physiological factors, and literally hundreds of dietary and behavioral modifiers that affect the disease process in one way or another (7–9). However, despite the daunting number of variables, chronic inflammation appears to function as a common etiologic mechanism, contradicting the established view of obesity and metabolic syndrome as purely metabolic disorders (10–13). As such, much investigation has focused on the etiology and effectors of inflammation. Studies completed in the past decade have highlighted the central role of tissue-associated bone marrow-derived macrophages in coordinating both the metabolic and inflammatory aspects of metabolic syndrome (14; 15). However, despite the recent progress made in elucidating the role of these cells, relatively little is known about their homeostatic functions beyond their role in disease.

In this review, we will briefly summarize the literature regarding inflammatory insulin resistance in metabolic syndrome, discuss the protective role played by alternatively activated macrophages (AAMs), and discuss the therapeutic implications there of. We argue that inflammation is only a portion of the larger functionality of the tissue macrophage and that metabolic syndrome is thus a derangement of macrophage activation characterized by both a deleterious state of chronic inflammation and loss of positive trophic signals.

FUELING IMMUNITY

To fully appreciate the complex dialogue between the immune system and metabolic tissues, we must first review the mechanisms by which the immune system protects the host against potential pathogens. In vertebrates, a layered immune defense system protects against unwanted intrusion (16). Passive barriers and recruited microbial allies comprise the outer curtain of defense—epithelial and mucus barriers, commensal competition, and chemically inhospitable gateways (e.g. the stomach) dissuade the vast majority of unwanted guests (17). For intruders that penetrate these barriers, the active immune response, comprising both innate and adaptive responses, presents an inner defense (16). The innate immune response, comprised of a host of cell types including neutrophils, eosinophils, mast cells, and macrophages, is the first of the active defenses that respond to any intrusion (17; 18). These cells are present throughout the entire organism—with special attention paid to those passive barriers mentioned above—continuously sampling their local tissue microenvironments for evidence of potential pathogens. To stand ready for any one of the myriad forms of invader, vertebrate genomes encode a variety of pathogen-associated molecular pattern (PAMP) receptors, e.g. Toll-like receptors (TLRs), which recognize and categorize threats into broad classes and mount the appropriate responses appropriate (17). For the small, highly replicative bacterial trespasser, robustly phagocytic neutrophils armed with toxic reactive

oxygen and nitrogen species mount a localized, intense, and highly destructive response to quickly halt the rapid spread of these organisms. This response, however, would be entirely ineffective against larger pathogens such as helminths, with their own passive barriers, large size, and relative indifference towards toxic insult. In this instance, PAMP-driven innate responses tend towards eosinophil-coordinated mucus barriers and gastrointestinal/respiratory expulsion (19). While these responses are generally successful, they are often incapable of completely eradicating the offending organism. The continued persistence of an antigenic stimulus triggers the activation and deployment of the adaptive immune response. In contrast to the immediate and semi-specific responses of the innate immune response, the adaptive immune system takes 4–7 days of gene rearrangement and somatic hypermutation to fully deploy and results in highly-specific antibody and effector lymphocyte responses against specific molecular epitopes on offending organisms that persist for years after the interloper's eradication (16; 18; 20).

The spectrum of immune response evinces an impressive range of intensity, from the hours-long half-life of neutrophils to the decades-long persistence of memory lymphocytes. Until recently, this spectrum was viewed as just another curiosity in an impressive list of immune system statistics; however, recent work has defined that unexpectedly complex metabolic programs are necessary for these divergent roles. Moreover, these studies have also defined an instructional role for these same "provisional" metabolic programs in guiding and shaping the immune response, establishing a paradigm in which cellular metabolism and immune activation are intimately linked, both requiring the other for full execution (21–24). Indeed, the curious anatomic juxtaposition of immune and metabolically critical cell types, recognized for decades but unexplained by host defense theory, provides an architectural framework for direct communication between the two putatively unrelated yet evolutionarily fundamental systems (11). For example, lymph nodes—the local command and operation centers for the adaptive immune system—are embedded in depots of white adipose tissue (perinodal adipose tissue or PAT), which provide a dedicated source of metabolic substrate for fueling immune activation (25). Interestingly, studies of single lymph nodes have demonstrated that the composition of lipids provided by the PAT differs tremendously from those provided by neighboring adipose tissue just distal to the node (26). Specifically, the PAT of resting lymph nodes is dominated by polyunsaturated fatty acids, whereas their concentration is much less in neighboring adipose tissue. Under conditions of prolonged inflammatory activation of the lymph node, however, the lipid composition shifts to provide large amounts of saturated fatty acids and glycerol, metabolic substrates for which inflammatory cells have a known predilection. Intriguingly, in vitro studies have demonstrated the capacity of these same lipid mixtures to induce the quiescent or inflammatory profiles with which they are associated in vivo, independent of any immune signals. These observations define a mutual coordinated network of instructive and provisional signals between immune and metabolic cell types.

The anatomic and functional juxtaposition of immunity and metabolism is obvious in central metabolic tissues as well: the liver and white adipose tissue—the two primary players in mammalian energy homeostasis—are densely populated by representatives of both the adaptive and innate immune systems whose activation states and behaviors vary with varying metabolic circumstance (11). For instance, obesity is associated with a dramatic decrease in the number of natural killer T (NKT) cells in the liver (27), while the same metabolic variance is accompanied by an increase in activated T cells in white adipose tissue (28). However, despite the presence and functional contributions of lymphocytes, neutrophils, eosinophils, mast cells, and even the enigmatic basophil to metabolic tissue homeostasis, it is the macrophage that is both numerically and functionally dominant.

MACROPHAGE ACTIVATION

Macrophages are highly heterogeneous hematopoietic cells found in nearly every tissue in the body (29). Canonically, these cells have been defined as the sentinels of the innate immune system, monitoring the varied tissue milieu for early signs of infection or tissue damage. In this role, the macrophage is responsible for sensing, integrating, and appropriately responding to a bewildering array of stimuli from its local microenvironment. Despite the daunting array of inputs, macrophage responses are coordinated through two distinct and mutually exclusive activation programs, termed classical (or M1) and alternative (or M2) (30; 31). These activation programs were initially defined by their antimicrobial activities: classical activation occurs in response to products derived from or associated with bacterial infections, such as lipopolysaccharide (LPS) and interferon gamma (IFNγ), and results in highly inflammatory macrophages with high phagocytic and bactericidal potential (30; 32) (Figure 1a). In contrast, alternative activation occurs in response to products derived from or associated with parasitic infections, such as *Schistosoma* egg antigen and interleukins (IL)-4 and -13, and promotes antiparasitic functionalities as well as those involved in tissue repair and remodeling (33) (Figure 1b). Both programs promote differentiation of neighboring macrophages to their same activation state and potently inhibit maturation of the other. A large number of differentially expressed markers have been identified by which the two activation states can be discriminated; however, the differential metabolism of arginine is perhaps the most well-defined and reliable of them (33). In the classically activated macrophage (CAM), arginine is catabolized to bactericidal nitric oxide and citrulline via the induction of inducible nitric oxide synthase (Nos2), whereas the alternatively activated macrophage (AAM), by contrast, upregulates arginase 1, which produces the polyamine precursor urea and ornithine, necessary for collagen synthesis and cellular proliferation, respectively (34; 35) (Figure 1c).

While these activation states were defined initially by their function in host defense, further study has revealed additional roles for them in health and disease. As mentioned previously, the alternative phenotype has been implicated in wound healing, tissue remodeling, atopic disease states, and apoptotic cell disposal, whereas the classical phenotype has been shown to play a causal role in inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis (30). One of the most interesting areas in which the dichotomy between classical and alternative activation has been studied, however, is that of energy homeostasis and metabolic disease (23).

INFLAMMATION AND INSULIN RESISTANCE

As mentioned in the introduction, metabolic diseases, including obesity, insulin resistance and type 2 diabetes, are driven by a chronic, low-grade inflammatory state that contributes directly to their induction, maintenance, and escalation (12; 13; 36). This state is characterized by elevated serum levels of proinflammatory cytokines (e.g. IL-1, IL-6, IL-8, IL-12, and TNFα), chemokines (e.g. MCP-1, RANTES, and MIP-1), acute phase reactants (e.g. C-reactive protein, serum amyloid A, and ferritin), insulin resistance-associated adipokines (e.g. retinol binding protein-4 and resistin), procoagulative factors (e.g. PAI-1), and hypertensive agents (e.g. angiotensinogen) and with decreased serum levels of the so-called “negative” acute phase reactants (e.g. transcortin, and transferrin), insulin sensitivity-associated adipokines (e.g. adiponectin, visfatin, omentin, and vaspin) (12; 13; 36). Indeed, infusion of proinflammatory mediators, such as TNFα, alone is sufficient to recreate the insulin resistant phenotype observed in animal models fed a high-fat diet and to promote obesity (37), whereas genetic deletion of these same mediators greatly attenuate the diet’s deleterious effects (38). Congruent with these findings, central regulators of inflammation, including NF-κB and jun N-terminal kinase (JNK1), are chronically activated in adipose

tissue from obese and insulin resistant subjects (12; 13; 36). Interestingly, these same tissues show abnormal inhibitory serine phosphorylation of critical insulin receptor substrates, suggesting a possible mechanism by which kinases in inflammatory signaling pathways could directly impinge upon insulin signaling. Indeed, JNK1 and inhibitor of NF-κB-kinase β (IKKβ, an NF-κB-activating kinase) both directly phosphorylate serine residues on insulin receptor substrate 1 (IRS1), the major downstream effector of the insulin receptor, in response to TNFα stimulation (37; 39; 40) (Figure 2).

These observations provide a direct mechanism by which inflammation subverts insulin signaling in a self-sustaining manner, but they fail to explain exactly how well-known behavioral and dietary indiscretions initiate this inflammatory brew. The well-described acquisition of an inflammatory phenotype somewhere along the trajectory to obesity suggests the appearance of at least one inflammatory stimulus during the process. Indeed, there is evidence for multiple sources that contribute to both initiation and propagation of inflammation within liver and white adipose tissue. For example, Flier et al astutely recognized the structural similarities between saturated fatty acids, a known dietary risk factor for insulin resistance, and immunogenic components of bacterially-derived lipids such as LPS. They hypothesized that the elevated levels of saturated fatty acids present in obesity are able to activate TLR4, the cell-surface receptor activated by LPS, and initiate an inflammatory response (41). Indeed, high concentrations of dietary saturated fatty acids are able to activate TLR4 in vitro and in vivo, and animals lacking TLR4 are protected from high-fat diet-induced insulin resistance (41–43). Furthermore, infusion of saturated fatty acids is sufficient to induce insulin resistance in lean animals in a TLR4-dependent manner. Interestingly, ligation of TLR4 directly activates the JNK1 and NFκB signaling pathways, providing a direct mechanistic link between diet and insulin resistance vis-à-vis elevated saturated fatty acids (41; 42; 44; 45) (Figure 23).

A second link between dietary excess and insulin resistance was uncovered through study of the endoplasmic reticulum (ER) stress response (11). During conditions of high circulating nutrient levels, such as those which occur post-prandially, glucose and fatty acids are stored as triglycerides in the adipocyte for later use. However, in chronically over-fed states, this storage/buffer capacity is exceeded, and excess free-fatty acids leak into the cytoplasm of the adipocyte and into circulation. Hotamisligil and colleagues demonstrated that elevated intracellular concentrations of these free fatty acids lead to ER stress and activation of downstream signaling pathways, including JNK1, that contribute to the development of insulin resistance (46; 47) (Figures 2, 3). Furthermore, administration of chemical chaperones known to reduce ER stress alleviates diet-induced insulin resistance (48; 49); whereas genetic inactivation of the ER stress response leads to its exacerbation (47). These findings provide a second mechanism linking inflammatory insulin resistance with caloric excess (Figure 3).

Thirdly, the robust hypertrophy of adipocytes in obesity is also accompanied by adipose tissue hyperplasia. Unlike the exercise-associated corollary in skeletal muscle, however, adipose tissue hyperplasia does not take place in a highly vascularized tissue nor does angiogenesis keep pace with the process. As such, the rapidly-expanding visceral adipose depots out-strip their vascular supply, resulting in hypoxia that synergizes with ER-stress to lead to increased rates of adipocyte necrosis (50; 51). As opposed to immunologically silent apoptosis, necrotic cell death is highly phlogistic, triggering inflammatory activation of macrophages in addition to other related cell types (52) (Figure 3). Even in those cells that survive, hypoxia activates HIF-1α, which results in the elaboration of the same pro-inflammatory mediators implicated in insulin resistance.

CLASSICAL MACROPHAGE ACTIVATION PROMOTES INSULIN RESISTANCE

While elevated saturated fatty acids levels, ER stress, and tissue hypoxia necessarily originate with the adipocyte, the tissue macrophage is the primary cell responsible for mounting and maintaining the inflammatory response and, as such, represents the nexus of adipose tissue inflammation (Figure 3). Ferrante, Chen and colleagues were the first to observe that macrophage representation within white adipose tissue increases with increasing adiposity, indicating that recruitment and infiltration of new, bone marrow-derived macrophages into the adipose tissue also increased with adiposity (14; 15) (Figure 4). The expansion in representation from 10% to over 50% of total cell number, when accompanied by 5-fold or more increase in overall adipose tissue mass that necessarily accompanies obesity, dictates that nearly all adipose tissue macrophages (ATMs) in obese individuals are recruited after the onset of weight gain. Ferrante and colleagues suggested that blocking the recruitment and infiltration of pro-inflammatory blood monocytes into adipose tissue would then selectively impair ATM inflammatory activation without affecting other myeloid populations or tissue beds. Previous work had demonstrated that C-C motif chemokine receptor-2 (CCR2)-positive blood monocytes are selectively recruited to sites of inflammation where these cells, but not $CCR2^{-}$ monocytes, differentiate into pro-inflammatory tissue macrophages (53). Studies with CCR2 deficient mice demonstrated that recruitment of pro-inflammatory monocytes to adipose tissue was sufficient to protect mice against diet-induced insulin resistance (54). By contrast, animals overexpressing MCP1 in the adipocyte exhibit increased susceptibility to insulin resistance and obesity (55; 56). Thus, the systemic metabolic and inflammatory improvements observed in these models confirm the role of inflammatory ATMs in paracrine and endocrine metabolic regulation.

Further evidence supporting the central role of tissue macrophages was provided by global and lineage-specific genetic ablation of transcriptional mediators of inflammation. Consistent with its pivotal roles in inflammatory insulin resistance, global deletion of *Mapk8* (the gene encoding JNK1) resulted in marked protection from diet-induced obesity and insulin resistance (57). Interestingly, hepatic deletion of *Ikbkb* (the gene encoding IKKβ, a kinase required for NF-κB activation) prevented the development of inflammation and insulin resistance solely in this depot, suggesting that the systemic inflammatory milieu encountered in obese subjects is the product of multiple local phenomena rather than a coordinated systemic condition (58; 59).

In addition to providing definitive evidence of inflammation's role in insulin resistance, these studies also provide an avenue for distinguishing the contribution of macrophage inflammation from that of adipocytes and hepatocytes as well as from that of other infiltrating leukocytes. Using reciprocal adoptive transfer to create chimeric animals, Karin et al were able to demonstrate that JNK1 deletion from nonhematopoietic cells is sufficient to protect mice from diet-induced obesity and, indirectly, from concomitant insulin resistance (60). By contrast, deletion of JNK1 from the hematopoietic compartment decreases hepatic and adipose tissue inflammation and improves insulin sensitivity without affecting adiposity, suggesting that diet-induced inflammation, not obesity, is directly responsible for insulin resistance and mediated primarily by bone marrow-derived cells (60). Furthermore, myeloid-specific deletion of IKKβ utilizing a cre-lox approach is sufficient to dramatically reduce inflammation, similar to loss of JNK1 from the entire hematopoietic compartment (58). Given the relative paucity of other myeloid lineages in adipose tissue and the liver, these data strongly suggest macrophages as the primary source of diet-induced inflammation in these tissues.

ALTERNATIVE MACROPHAGE ACTIVATION ENHANCES INSULIN ACTION

These studies define much of inflammatory insulin resistance and place the macrophage in the pathogenic role of inflammatory instigator. Several lines of evidence, however, suggest that this is an overly simplified model. For example, while macrophage representation in adipose tissue increases with increasing adiposity, representation in the liver does not, nor is the adipose tissue of lean individuals bereft of macrophages. Moreover, despite the marked phenotype, ATM numbers are only moderately reduced in the $CCR2^{-/-}$ animals that lack the ability to recruit inflammatory macrophages. Indeed, the non-linear relationship between macrophage number and behavior suggests that tissue macrophages have a greater functional repertoire than simple inflammation.

The first evidence to suggest diversity in the metabolic tissue-associated macrophage pool came from differential profiling studies of adipose tissue from lean and obese mice. Saltiel and colleagues demonstrated that ATMs from lean mice, rather than being quiescent or mildly inflammatory, are activated along the alternative pathway (61) (Figure 4). Similarly, Kupffer cells (the resident tissue macrophages of the liver) from lean animals express high levels of alternative markers, which are swapped for an inflammatory profile in obesity (62; 63).

Based on the ability of AAMs to restrain their classically activated brethren, their presence in the adipose tissue and liver of lean animals strongly suggests that they play a role in preventing inflammatory insulin resistance. Despite this promise, the paucity of knowledge regarding the biology of AAMs hindered its exploration.

To explore the biological relevance of these findings, our laboratory exploited the overlapping provisional and instructive roles of metabolism in immune activation to identify transcriptional machinery necessary for alternative activation. Unlike classical activation, where functions are executed over hours to days, alternative activation is purposed for long-term activities with functional lifetimes of months. The dramatic difference in time scale suggests distinct metabolic provisional requirements. Indeed, while classical activation of macrophages induces a glycolytic program capable of rapidly providing the energy and reducing equivalents necessary for intense, short-lived bactericidal activity (64; 65), alternative activation opts for a more efficient program of fatty acid oxidation and oxidative glucose metabolism capable of being sustained for long periods of time (65). Furthermore, blocking oxidative metabolism not only selectively abrogates the cell's ability to undergo alternative activation but also potentiates expression of the classical program. Conversely, forcing the macrophage down the oxidative route by overexpressing PGC-1β, a key transcriptional proponent of oxidative metabolism, potentiates alternative activation and prevented classical (65). As such, metabolism operates as both a provisional and instructive cue for macrophage activation (Figure 5).

Not surprisingly, these approaches identified activation of STAT6, IL-4's well-studied transcriptional effector, as the critical initiating event in macrophage alternative activation (65); however, peroxisome proliferator-activated receptor (PPAR)-γ and -δ, the body's fatty acid sensors, were identified as responsible for sustaining it (62; 63; 66) (Figure 5). These proteins were both shown to bind to and directly regulate the activity of genes critical to alternative activation in an overlapping but non-redundant manner. While PPARγ directly regulates its associated metabolic program (66), PPARδ coordinates the immunologic effector functions of alternative activation, including expression of pattern-recognition receptors and co-stimulatory molecules, as well as suppression of the inflammatory response (62; 63). Importantly, unsaturated dietary fatty acids such as oleic acid synergize with IL-4 to drive the alternative response by acting as metabolic substrates as well as transcriptionally

activating PPARδ (63) (Figure 6). These findings complement those mentioned previously in which unsaturated fatty acids possessed anti-inflammatory properties, providing a mechanism by which unsaturated fatty acids promote macrophage alternative activation and antagonism of the classical phenotype. Additionally, these findings potentially explain why dietary shifts from foods rich in unsaturated fatty acids to those rich in saturated are associated with the acquisition of an inflammatory phenotype within lipid-rich tissues.

Utilizing these insights, we developed two mouse models in which macrophage alternative activation was severely compromised: in the first, PPARγ was selectively deleted from the myeloid compartment utilizing cre-lox technology (PPARγ-LysMCre); in the second, PPARδ$^{-/-}$ bone marrow was adoptively transferred into irradiated wild-type mice to generate animals lacking PPARδ in hematopoietic cells only (PPARδ-BMT). Bone marrow- and tissue-derived macrophages from both strains of mice are markedly impaired in alternative activation as assessed by in vivo transcriptional profiling, ex vivo stimulation, and in vivo functionality (63; 66). Importantly, both strains of mice display significantly higher expression of inflammatory markers, increased weight gain, and reduced insulin sensitivity than their wild-type counterparts when fed a high-fat diet (62; 63; 66; 67). While the systemic effects of these interventions are similar, there is an interesting discordance in tissue specificity: the inflammatory changes present in PPARγ-LysMCre mice are most marked in visceral white adipose tissue, while those of PPARδ-BMT mice were most prominent in the liver (63; 66). The discrepancy between these results may reflect divergent roles for PPARγ and δ in Kupffer cell and ATM biology; however, it may also be explained by differences in strain (Balb/cJ vs. Sv129/J, respectively) and experimental design (cre-lox vs. adoptive transfer) as cre-lox abrogation of myeloid PPARδ produced a phenotype more similar to that of the PPARγ-LysMCre mouse than that of the PPARδ-BMT (62). Additionally, Tontonoz et al observed no significant difference between mice lacking myeloid PPARγ, PPARδ, or both and wild-type controls on the more M1-prone C57/B6 background, further supporting a role for strain dependence (68).

REGULATION OF ALTERNATIVE MACROPHAGE ACTIVATION IN METABOLIC TISSUES

These studies identify a critical homeostatic role for macrophage alternative activation in metabolic tissues. Additionally, they provide insight into mechanisms by which this protective role is effected. Since its identification as a distinct functional state, alternative activation has been largely defined by its ability to antagonize and inhibit classical activation and the associated phlogistic sequelae (30; 31; 69). As these sequelae include insulin resistance, the functional aspect of macrophage alternative activation that has received the most attention has been its anti-inflammatory properties (Figure 6). Indeed, multiple studies have demonstrated that any impairment of macrophage alternative activation exacerbates expression of inflammatory markers within liver and adipose tissue (61–63; 66; 70). Additionally, in vitro and ex vivo studies have demonstrated the ability of AAMs to inhibit inflammatory mediator expression in both classically activated macrophages (CAMs) and other leukocytes, as well as in adipocytes and hepatocytes themselves. Complementary to these findings, a recent study demonstrated that IL-10-producing AAMs also restrain diet-induced adipose tissue inflammation through the induction of regulatory T cells (71).

Additionally, AAMs have been implicated in a number of tissue maintenance roles that function to limit cellular damage, which would otherwise result in inflammation and, concomitantly, insulin resistance (Figure 6). For example, adipose tissue undergoes striking hyperplasia during the development of obesity. Alternatively activated macrophages are crucial for the vascular and structural remodeling necessary to prevent ischemia and overcrowding (30; 31). Indeed, chronically inflamed adipose tissue demonstrates larger

hypoxic zones and higher levels of expression of hypoxia-associated genes including those that promote inflammatory activation, such as HIF-1α (50; 51; 72). Complementary studies have demonstrated that PPARδ, which controls alternative macrophage activation, is also critically involved in immunologically silent disposal of those cells that do die, whether from hypoxia or other causes (73). Indeed, inflamed adipose tissue contains inflammatory cells associated with dying adipocytes—so-called crown-like structures—whereas these complexes are not observed in adipose tissue from lean insulin-sensitive animals (74; 75).

While studies of the anti-inflammatory properties of AAMs have yielded much information regarding their protective role in diet-induced insulin resistance, the view of AAMs as simple antagonists of their classically activated counterparts, or even of leukocyte- and parenchyma-derived inflammation alike, is overly simplistic. Indeed, several lines of evidence suggest that there are roles for AAMs unrelated to inflammation (76). For example, obesity is defined by massive expansion of white adipose tissue depots, a process that necessarily involves extensive remodeling of not only the tissue vasculature, as discussed above, but also the adipose tissue itself. Without proper hypertrophy of white adipose tissue, chronic overnutrition rapidly leads to lipodystrophy, a condition of ectopic and non-specific lipid deposition throughout the body (72). Congruent with these findings, lipodystrophy is strongly correlated in both mice and humans with an absence of alternative activation signatures in white adipose tissue accompanied by an over-expression of classical phenotype (23).

The hepatic response to high-fat diets similarly evinces a homeostatic role for macrophage alternation activation. Under eucaloric conditions, the liver packages and exports dietary lipids for peripheral use or storage in white adipose tissue. When fed a high-fat diet, this export capacity can become overwhelmed, resulting in dystrophic lipid storage within the hepatocytes themselves. As in adipocytes, dystrophic lipid storage results in elevated cytoplasmic free fatty acids and activation of inflammatory pathways through the ER stress response or TLR ligation (77; 78). If the dietary stress is not relieved, the liver develops non-alcoholic steatohepatitis (NASH, a condition marked by hepatic inflammation and hepatocytes necrosis), which can progress to cirrhosis and, rarely, hepatocellular carcinoma (79). Animal models with impairments in macrophage alternative activation (e.g. PPARδ$^{-/-}$ BMT, and PPARδ-LysMCre mice) develop more severe NASH than wild-type controls when exposed to a high-fat diet (62; 63). Interestingly, however, ablation of the entire Kupffer cell population causes mice to develop a similar phenotype despite a reduction in hepatic inflammation (80–82). These data demonstrate that while macrophage-derived inflammation may drive steatohepatitis, the alternative macrophage phenotype is necessary for proper hepatocellular lipid handling (83).

The prevalence of AAMs in metabolic tissues and the importance of their homeostatic roles raise a key question: what drives this alternative polarization in lean animals? While the answer to this question remains unknown, several lines of evidence suggest that it is an integration of immunologic and metabolic signals. First, while saturated fatty acids dominate in obese, insulin-resistant individuals, unsaturated fatty acids are the predominant free lipid in both metabolic tissues and in the circulation of lean subjects (84). These same unsaturated fatty acids activate PPARδ, while rising saturated fatty acids concentrations inhibit PPARδ transcriptional activity even as they activate antagonistic, pro-inflammatory pathways via ligation of TLR4 (41; 44; 63) (Figures 3 and 6). Furthermore, specific unsaturated fatty acids (e.g. n-3 PUFA) contribute to the formation of resolvins and protectins, lipid-based antagonists of inflammatory activation (85). As described above, a similar transition in free fatty acid composition takes place between lymph node lymphocytes and perinodal adipocytes following chronic inflammatory activation.

A second, compatible mechanism for biasing resident macrophages is suggested by studies of the adipokine adiponectin and its effects in macrophages (86) (Figure 6). Early studies of adiponectin describe its ability to promote oxidative metabolism in target cells (87; 88), including the macrophage (89). This induction of oxidative metabolism, as discussed above, effectively polarizes the macrophage towards alternative activation via dual-role transcriptional mediators such as PPARγ and δ.

While much of the alternative phenotype may be due to non-canonical signals through metabolic lines of communication, direct stimulation by Th2 cytokines form a third contributing factor. Lee et al have reported low-level expression of both IL-4 and -13 in adipocytes and hepatocytes and correlated this with lean, insulin sensitive phenotypes (62). While this expression level is not sufficient to be detected in circulation, these cytokines function in a paracrine manner to influence macrophages within the local microenvironment. Addition studies utilizing IL4-reporter mice are necessary to identify the cellular sources of IL-4 in liver and adipose tissue (90) (Figure 6).

THERAPEUTIC IMPLICATIONS

Our increased understanding of the complex regulatory relationship between immune and metabolic cell types has engendered interest in exploiting this relationship to address the mounting threat of metabolic disease. Undeniably, the most effective manipulation of this relationship is accomplished by lifestyle modification. Dietary replacement of saturated fats and refined sugars by unsaturated fats and complex carbohydrates, as seen in Mediterranean diets for example, replaces a pro-inflammatory stimulus with an anti-inflammatory one, as outlined above, and is, unsurprisingly, associated with improvements in inflammation and insulin resistance (91–93). Normalization of caloric intake is similarly associated with improvement in insulin resistance, largely through decreased adiposity. Exercise also operates through weight reduction, though it additionally promotes anti-inflammatory tone and suppresses chronic inflammation independent of weight loss (94; 95).

Despite the relative simplicity and undeniable efficacy of lifestyle interventions, persistent public disinterest in this approach has refocused attention on pharmacologic adjuncts. Unfortunately, the redundant and positively reinforcing quagmire that is metabolic syndrome—not to mention our desire for high-calorie food and lots of it—has largely thwarted initial efforts. These efforts can be divided into four main categories: 1) intake inhibition (e.g. appetite suppressants, malabsorptive agents, bariatric surgery), 2) output augmentation (e.g. stimulants), 3) immunosuppression, and 4) immunomodulation. The first two categories are solely based on thermodynamic arguments and as such will not be discussed here. Instead we will focus on the two latter approaches, both of which exploit the relationship between immune function and metabolism.

Not surprisingly, the first therapies targeting the immune component of obesity and metabolic syndrome were designed to broadly inhibit immune function. Our rudimentary early understanding of inflammation's role in insulin resistance suggested that removing immune influences over metabolic tissues would prevent their detrimental influence. Without knowledge of the pathophysiologic mechanisms of metabolic disease, Williamson and Lond first demonstrated more than a century ago that high-dose salicylate treatment reduced the severity of glycosuria in diabetic patients (96). Fifty years later, Reid and colleagues further demonstrated that aspirin treatment improved oral glucose tolerance test results in diabetic patients (97). The modern interpretation of these experiments is that the salicylates operate through direct inhibition of IKKβ, a known mediator of inflammatory insulin resistance (98–100). While the adverse effects of the salicylate doses required for meaningful pharmacological effect prevent their clinical adoption, targeted biologics have

revived interest in this approach. Systemic TNFα blockade with biologics such as infliximab and entanercept have shown promising results in animal models; however, results have been disappointing in early prospective trials in diabetic patients and mixed in retrospective studies of patients taking the drugs for inflammatory conditions such as psoriasis and rheumatoid arthritis (101; 102). These mixed results may be the result of a failure of these interventions to adequately neutralize inflammation in the liver and adipose tissue microenvironments. Alternatively, their failure may be understood in the context of our discussion above regarding the complexity of macrophage function in metabolic syndrome —metabolic health is not defined solely by the absence of systemic inflammation. Inhibition of pathologic inflammation alone may not be sufficient to replace the positive trophic influences lost with the alternatively activated macrophage pool.

Therapies directed at biasing the immune system rather than inhibiting it, also known as immunomodulation, represent a more nuanced approach, integrating the needs to both blunt pathologic classical activation and promote positive alternative activation. Though not as developed as traditional anti-inflammatory approaches, immunomodulatory therapies have demonstrated promise. Although unrecognized at the time, the first large-scale use of an immunomodulatory agent occurred with the introduction of the statins. Originally targeted at lowering cholesterol levels (103), statins have subsequently been shown to possess potent anti-inflammatory properties stemming from their unique ability to bias the immune response towards alternative activation via interference in isoprenoid biosynthesis (104; 105). Indeed, statin treatment of isolated dendritic cells in vitro leads to the cell autonomous upregulation of alternative markers, whereas treatment of uncommitted CD4+ helper T cells promotes Th2 maturation and the capacity to further alternatively bias uncommitted monocytes (106; 107). While their cholesterol-lowering properties are certainly important, their immunomodulatory capacity is thought to underlie much of the statins' cardioprotective properties (108–110). Indeed, statins have been shown to be effective in ameliorating inflammatory diseases as varied as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and graft-versus-host-disease (104). Observational studies have even described a chemopreventative effect for statins in the development of inflammatory-driven colorectal malignancies similar to that of non-steroidal anti-inflammatory drugs (111). Importantly, in contrast to the well-described adverse effects of current anti-inflammatory biologics, there is no evidence of any significant immunocompromise associated with their use. While most studies have focused on their cardioprotective effects, numerous studies have described mixed effects on insulin sensitivity despite reproducible improvements in inflammatory markers. Importantly, analysis of these reports demonstrates that certain statins (e.g. pravastatin, rosuvastation, fluvastatin) reproducibly improve insulin sensitivity independent of lipid lowering in obese subjects with and without diabetes (112–116), while others (e.g. simvastatin) consistently fail to do so despite similarly improvements in inflammatory markers (112; 115; 117). Interestingly, pravastatin therapy had no effect in lean, insulin sensitive patients, a population where previous studies have shown the alternative macrophage phenotype to be dominant (118). When taken together, these findings suggest that statins may exert their effects at least partly through the promotion of tissue macrophage alternative activation.

Another unintended foray into immunomodulatory therapy has been described in the murky field of nutrition and supplements. It has been long-appreciated that diets rich in unsaturated fatty acids are correlated with reduced chronic inflammation and its sequelae (91; 119), and recent studies discussed above (i.e. TLR4 ligation by saturated fatty acids and PPARδ ligation by unsaturated) have lent mechanistic validity to them. Large numbers of both cross-sectional and prospective studies have examined this question and while the results are somewhat mixed, the data generally support the conclusion that unsaturated fatty acids, especially n-3 polyunsaturated fatty acids, improve global insulin sensitivity, tend to

decrease adiposity, and significantly lower levels of serum inflammatory markers (91; 119; 120). These data, when taken together with the mechanistic data discussed above, suggest that the long-appreciated dietary wisdom serves, at least in part, an immunomodulatory function by promoting alternative immune responses.

While immunomodulation may exert its efficacy through macrophage deviation as a final common pathway, Dosch et al recently capitalized on the ability of T lymphocytes to direct macrophage function through a novel lymphocyte-directed approach (71). Recent studies have described a transition in the white adipose tissue-associated T lymphocyte population from protective Th2-biased helper cells to pathogenic Th1-biased helper and cytotoxic cells during the development of diet-induced obesity (71; 121; 122). This shift parallels the alternative-to-classical transition in macrophage activation, and together they describe a shift in the tissue microenvironment from anti-inflammatory to inflammatory with all of its attendant metabolic sequelae (Figure 3). Dosch and colleagues astutely recognized that eradication of adipose tissue-related lymphocytes from insulin resistant animals would reset the lymphocyte population and potentially redistribute the Th1/Th2 bias (71). Indeed, treatment with an anti-CD3 antibody erases the Th1-skewed T cell repertoire, and subsequent repopulation restores the T cell balance to something approximating that seen in lean animals. Furthermore, the reintroduction of regulatory and Th2 T cells re-directs the inflammatory macrophage profile to the alternative phenotype and results in dramatically decreases tissue inflammatory markers and results in sustained normalization of insulin sensitivity (71; 121; 123).

The evidence is clear that diet-induced insulin resistance is largely a disorder of deranged macrophage activation; however, efforts focused solely on inhibiting or correcting that derangement have fallen short of expectations. This is perhaps because once established, the metabolic derangements are self-sustaining and rely less upon continued inflammatory instigation, or alternatively, that these derangements provide their own inflammatory stimulation independent of immune function (e.g. high levels of saturated fatty acids can perpetuate insulin resistance in muscle and adipose tissue directly without intermediary leukocyte amplification). Regardless, it is likely that for any therapy to be effective in reversing established insulin resistance, it must target not only the driving mechanism of immune deviation but also the effector mechanisms of deranged skeletal muscle, liver, and adipose tissue metabolism. It is exactly this approach that is suggested by the discussion above: metabolic and immune functions not only communicate but also share certain transcriptional regulators, e.g. the PPARs, which are natural pharmacologic targets. Indeed, studies of synthetic PPARδ agonists have demonstrated great potential for use in metabolic syndrome: PPARδ activation not only promotes alternative macrophage activation and suppresses tissue inflammation (62; 63; 124), but also directly increases oxidative lipid catabolism in skeletal and cardiac muscle, adipose tissue, and liver; improves serum lipid profiles and global insulin sensitivity; and promotes weight loss in obesity (125).

PPARs

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. There are three PPARs (α, δ, and γ) in mice and humans, which control nearly all aspects of fatty acid metabolism. Rate-limiting enzymes involved in transport, synthesis, storage, mobilization, activation or oxidation of fatty acids are all regulated by PPARs. In a tissue- and stimulus-dependent manner, PPARs regulate distinct programs of fatty acid metabolism. PPARα regulates β- and ω-oxidation of fatty acids in the liver, whereas PPARδ regulates their oxidation in other peripheral tissues, including white adipose tissue, skeletal muscle and heart. In contrast, PPARγ is essential for long-term storage of

fatty acids as triglycerides in adipocytes. However, in macrophages, PPARγ is required for β-oxidation of fatty acids in response to IL-4.

PPARs regulate expression of their target genes through association with corepressor and coactivator proteins. Ligand binding results in a conformation change in the receptor, resulting in release of corepressor and recruitment of coactivator proteins. Endogenous ligands for PPARs include native and modified fatty acids, prostaglandins, leukotrienes and phospholipids. Fibric acids and thiazolidinediones are synthetic activators of PPARα and γ, and are currently used clinically to treat hypertriglyceridemia and type 2 diabetes mellitus, respectively.

Additionally, synthetic PPARγ ligands have been in clinical use for decades as insulin-sensitizing agents (126). These drugs were originally thought to operate through direct insulin sensitization of adipocytes (127–129); however, recent studies utilizing myeloid-specific deletion of PPARγ have demonstrated that the macrophage is an important site of action where they inhibit inflammation as well as promote the elaboration of insulin-sensitizing signals (67).

CONCLUSIONS

The rapid rise of humans from near-chronic starvation and universal parasitic infection to our current state of dietary excess and immunologic leisure has left our physiology feeling a bit dated. Not surprisingly, evolution paid little attention to the management of caloric excess and instead adapted to optimize caloric efficiency (130). Equally unexpected is that this optimal efficiency would be associated with the alternative immune phenotype associated with chronic infection with Th2-biasing parasites. Indeed, it seems that the twin threats of starvation and infection drove the co-evolution of the immune and metabolic systems into a single interconnected network with overlapping regulation and function. This system maintains homeostasis by harnessing the exquisite sensitivity and specificity of the immune system to regulate metabolic circumstance. As such, the alternative phenotype necessary to control chronic parasitic infections provides a basal stimulus directing optimally efficient oxidative metabolism. When the threat of an invading pathogen is detected, the inflammatory activation of the previously alternatively activated tissue macrophages rapidly induces an insulin-resistant metabolic state intended to shunt large amounts of glucose and other metabolic substrates into the periphery for unfettered use by the immune system to quickly eradicate the offending organism (23; 131).

In context of metabolic disease, the eradication of parasitic infections by modern sanitation has removed the basal alternative stimulus while our newfound caloric wealth and sedentary lifestyle provide novel stimuli misinterpreted as classical activation cues. The maladaptive constellation of responses mounted by our elegant yet somewhat anachronistic immune and metabolic systems is the metabolic syndrome.

This evolutionary perspective immediately suggests therapeutic strategies aimed at returning the immune and metabolic systems to their homeostatic states. Frequent exercise and balanced, eucaloric diets dominated by unsaturated fatty acids are the most obvious interventions as well as those most well-supported by experimental evidence. Rather than reintroducing parasitic infections, pharmacologic interventions such as those discussed above would serve to re-establish the alternative phenotype within inflamed tissues. Regardless of the approach, an appreciation of metabolic syndrome as a derangement of tissue macrophage activation will help guide future therapeutic strategies.

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ACRONYMS

AAMs	alternatively activated macrophages
CAMs	classically activated macrophages
LPS	lipopolysaccharide
TLR	toll-like receptor
BMT	bone marrow transplantation
ATMs	adipose tissue macrophages
PAMP	pathogen associated molecular patterns
TNFα	tumor necrosis factor α
NF-κB	nuclear factor κB
JNK	Jun N-terminal kinase
IKK	inhibitor of κB kinase
PPAR	peroxisome proliferator activated receptor
ER	endoplasmic reticulum
Th	T helper

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SUMMARY POINTS

- Obesity and metabolic syndrome are diseases of macrophage activation in adipose tissue and liver.
- Chronic inflammation is the common mechanism by which obesity and metabolic syndrome are initiated and sustained.
- Obesity and metabolic syndrome are accompanied by a shift in macrophage activation from the protective alternative state to the maladaptive classical response.
- Oxidative metabolism fuels alternative macrophage activation, a metabolic adaptation that is transcriptionally controlled by STAT6, PPARγ and PGC-1β.
- While IL-4/STAT6 signaling provides the instruction for alternative activation, PPARγ and δ signaling sustains this program of macrophage activation in metabolic tissues.
- Disruption of PPARγ or δ in myeloid cells impairs alternative activation in adipose tissue and liver, and worsens diet-induced metabolic disease.
- Obesity and metabolic syndrome are as much products of the loss of alternatively activated macrophages as the presence of classically activated macrophages.
- Pharmacologic approaches must address both the re-establishment of protective alternative functions as well as the inhibition of deleterious classical activities.

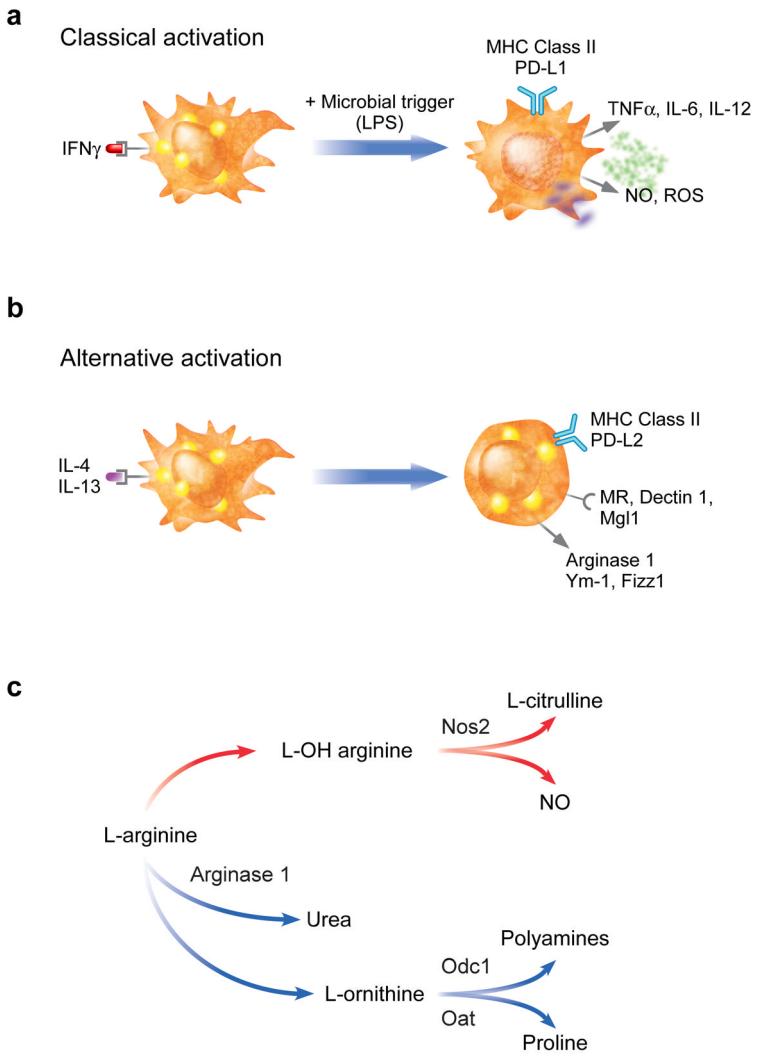

Figure 1. Classical and alternative macrophage activation

Macrophage activation comprises a broad spectrum of activities coordinated in response to specific environmental stimuli. While in reality a continuum, these responses can be separated into two basic patterns: classical, or M1, and alternative, or M2. **a)** Classical activation is a pro-inflammatory state purposed for the rapid destruction of bacterial invaders. Classically activated macrophages generate induce reactive oxygen species (ROS) and nitric oxide (NO) for their microbicidal actions, and secrete pro-inflammatory cytokines, such as TNFα and IL-12, to enhance cell mediated immunity. **b)** In contrast, alternative activation represents a more sustained response such as that typified by infection with parasites. While the induction of MHC class II and co-stimulatory molecules (PD-L2) indicate these macrophages are activated, they express a distinct repertoire of cell surface receptors (mannose receptor, *Mrc1*; dectin-1, *Clec7a*; and Mgl1, *Clec10A*), and secreted products (Ym-1, *Chi3l3*; and FIZZ1, *Retnla*). **c)** Differential metabolism of l-arginine in classically and alternatively activated macrophages by inducible nitric oxide synthase (Nos2) and arginase 1, respectively. Odc1: ornithine decarboxylase; Oat: ornithine aminotransferase.

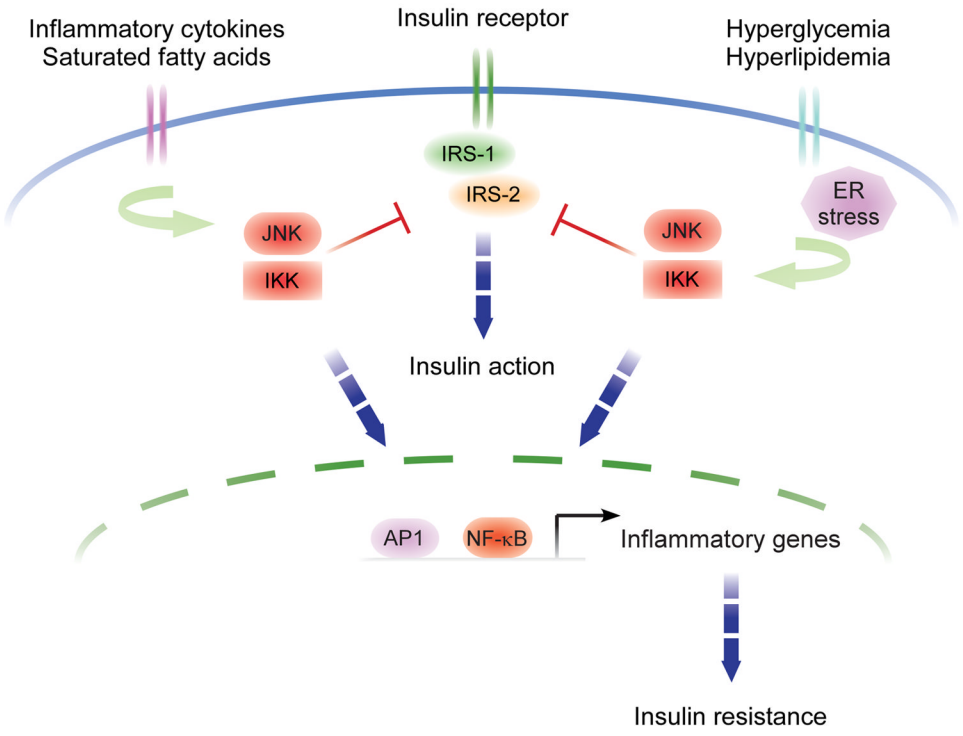

Figure 2. Intracellular mechanisms of inflammatory insulin resistance

Insulin action is transduced from the cell surface to cytoplasmic and nuclear responses via tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and -2. However, serine phosphorylation of these same substrates by JNK1 and IKKβ, the central mediators of stress and inflammatory responses, potently inhibits insulin action, thereby directly linking these responses to insulin resistance. In addition, the transcriptional activation of inflammatory genes by JNK1 and IKKβ induces insulin resistance in an autocrine and paracrine manner in tissues. Moreover, in states of obesity, JNK1 and IKKβ signaling pathways are activated by increased influx of free fatty acids and glucose.

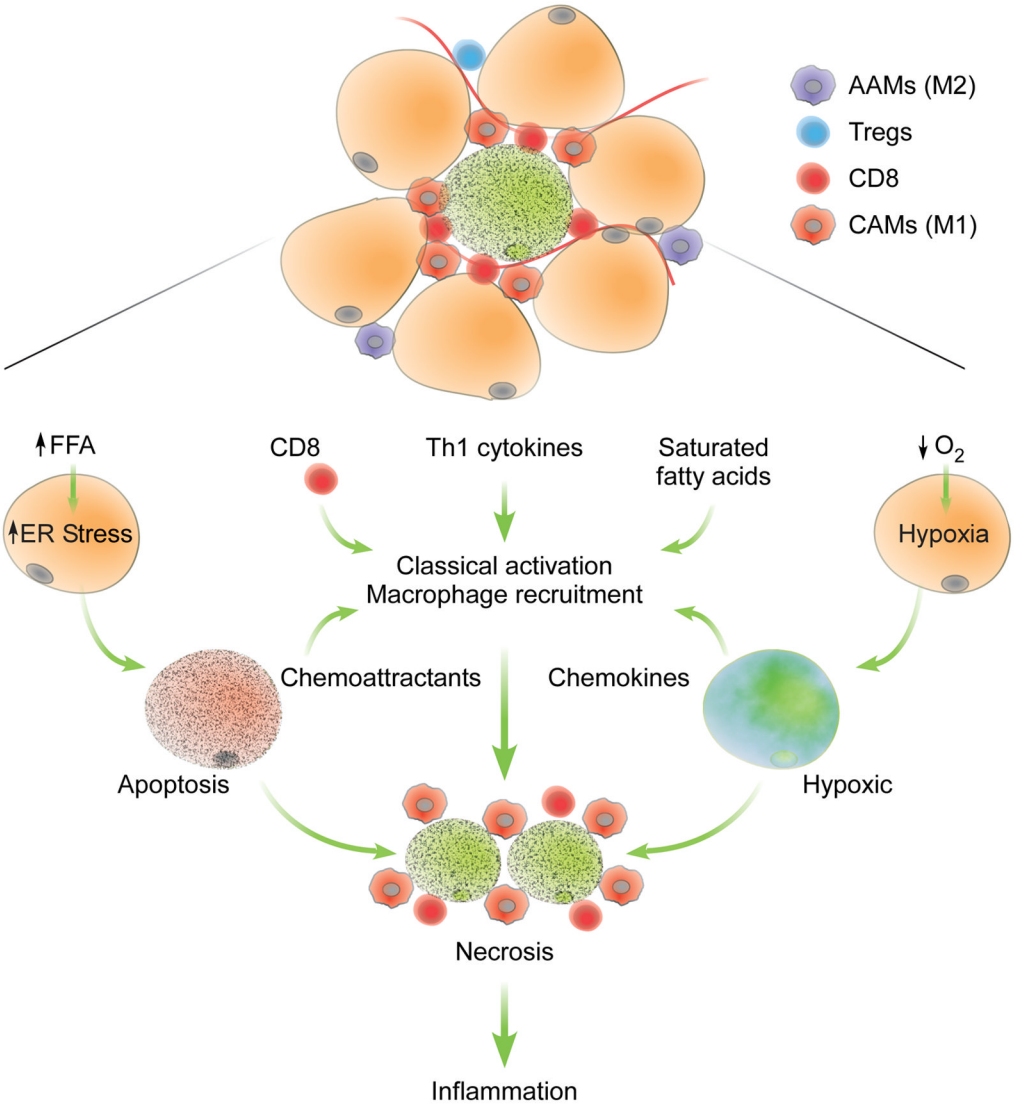

Figure 3. Factors controlling recruitment and classical activation of ATMs

Increased intake of diets rich in saturated fatty acids induces obesity, resulting in recruitment of CCR2+ monocytes that differentiate into classically activated macrophages. The inflammatory milieu that promotes classical activation (M1) of ATMs in obese animals includes recruitment of CD8 cells, reduction in numbers of regulatory T cells (Tregs), and increased production of Th1-type cytokines. In addition, adipocyte hypertrophy induces ER stress and hypoxia, factors that eventually lead to cellular necrosis. In obese animals, CD8 cells and CAMs form crown-like structures around necrotic adipocytes. The dramatic increase in CAMs in obese adipose tissue negates the anti-inflammatory and homeostatic functions of AAMs, resulting in increased inflammation. AAMs: alternatively activated macrophages; CAMs: classically activated macrophages.

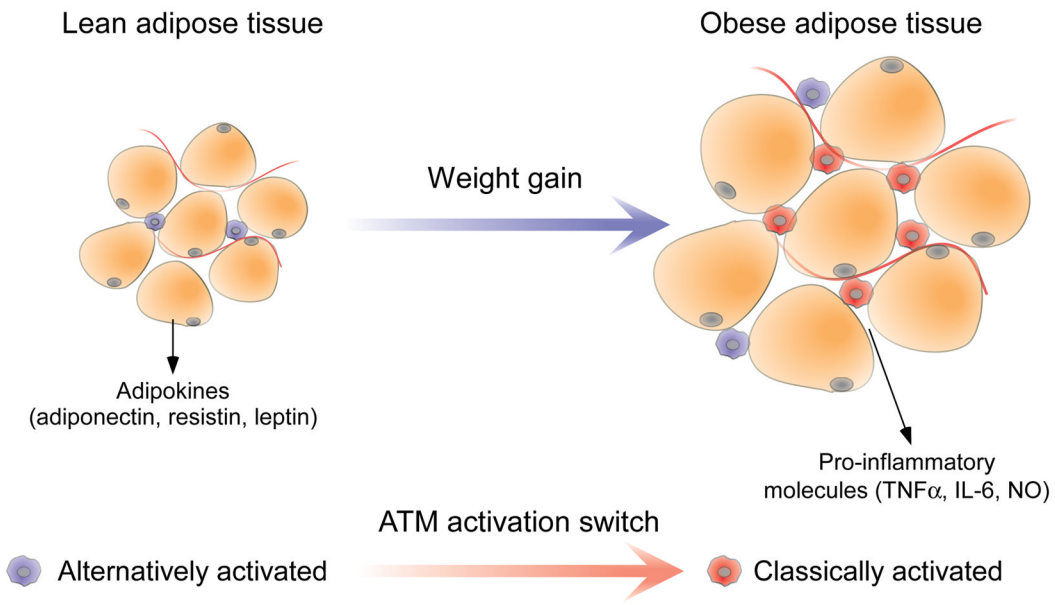

Figure 4. Functional differences between lean and obese adipose tissue

Adipose tissue from lean individuals comprises small, insulin-sensitive adipocytes that secrete large amounts of insulin-sensitizing adipokines under the influence of alternatively (M2)-biased adipose tissue macrophages (ATMs). In contrast, adipose tissue from obese individuals displays an expanded and prominently classically (M1)-biased population of ATMs, which secrete a variety of potent inflammatory mediators, together with hypertrophic, insulin-resistant adipocytes.

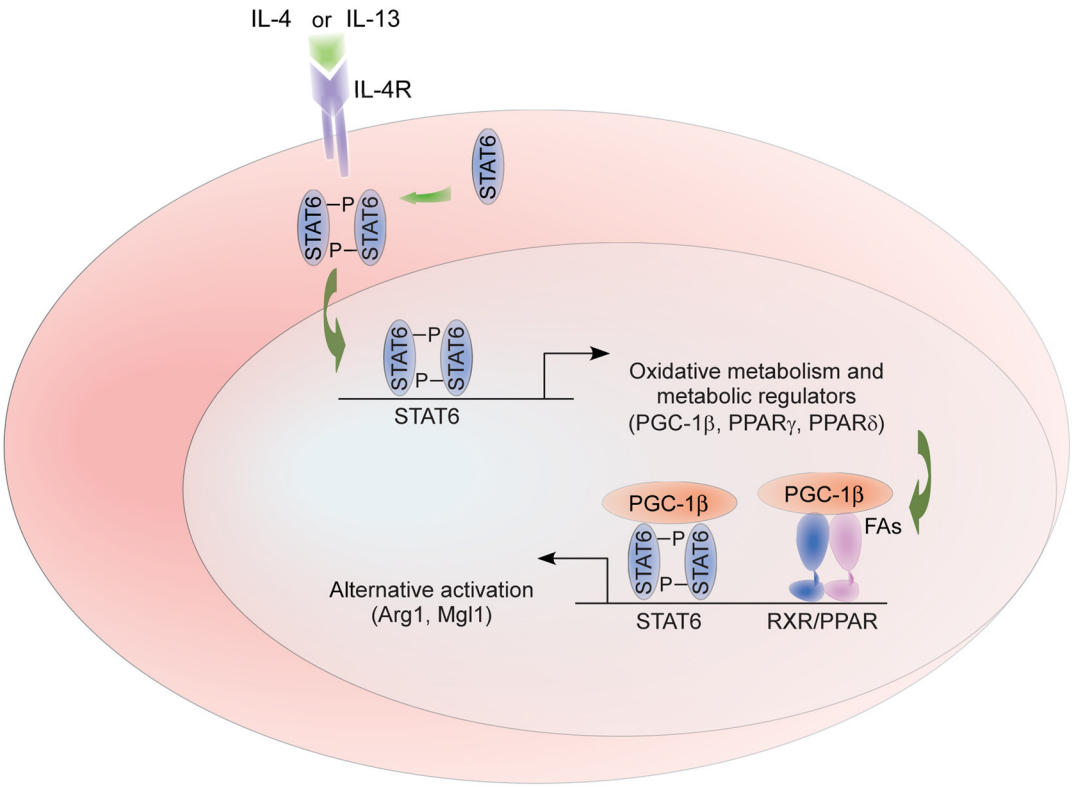

Figure 5. Transcriptional mechanisms controlling alternative (M2) activation

The canonical pathway of alternative macrophage activation involves activation of STAT6 by the Th2 cytokines IL-4 and -13. STAT6 activation initiates a transcriptional program comprising both immunologic effector responses and metabolic adaptations necessary to sustain them. Among the metabolic targets of STAT6 are PPARγ and δ as well as related coactivator PGC-1β. The transcriptional synergy between these metabolic regulators and STAT6 serves to sustain the immune effector response as well as direct metabolic adaptation for oxidative metabolism.

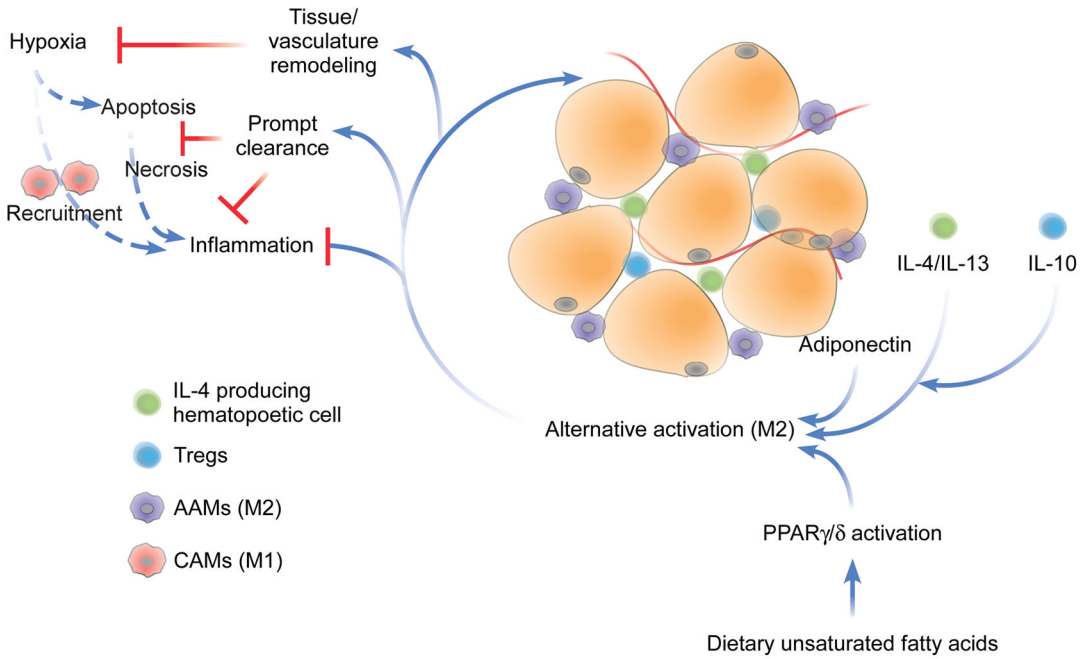

Figure 6. Effects of alternatively activated (M2) macrophages on adipose tissue

Dietary intake of unsaturated fatty acids and maintenance of lean body mass results in alternative activation (M2) of ATMs via activation of PPARγ/δ, local production of Th2 cytokines IL-4, IL-13, and IL-10, and release of trophic adipokines, such as adiponectin. The alternative phenotype protects against IR through the direct suppression of inflammation as well as through positive homeostatic maintenance activities, including remodeling of adipose tissue to prevent hypoxia and prompt clearance of apoptotic cells to prevent cellular necrosis. AAMs: alternatively activated macrophages; CAMs: classically activated macrophages.