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REVIEW

Research Progress Into Adipose Tissue Macrophages and Insulin Resistance

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Summary

In recent years, there has been an increasing incidence of metabolic syndrome, type 2 diabetes, and cardiovascular events related to insulin resistance. As one of the target organs for insulin, adipose tissue is essential for maintaining *in vivo* immune homeostasis and metabolic regulation. Currently, the specific adipose tissue mechanisms involved in insulin resistance remain incompletely understood. There is increasing evidence that the process of insulin resistance is mostly accompanied by a dramatic increase in the number and phenotypic changes of adipose tissue macrophages (ATMs). In this review, we discuss the origins and functions of ATMs, some regulatory factors of ATM phenotypes, and the mechanisms through which ATMs mediate insulin resistance. We explore how ATM phenotypes contribute to insulin resistance in adipose tissue. We expect that modulation of ATM phenotypes will provide a novel strategy for the treatment of diseases associated with insulin resistance.

Key words

Insulin resistance • Adipose tissue • Inflammation • Adipose tissue macrophages • Phenotype

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Introduction

Insulin resistance (IR) refers to a pathological state in which tissues such as adipose tissue, liver, and skeletal muscle, develop impaired sensitivity or responsiveness to insulin. IR is an important mechanism underlying the development of metabolic syndrome, type 2 diabetes mellitus (T2DM), cardiovascular events, and other diseases [1-3]. Its presence is characterized by a long-lasting chronic low-grade inflammatory state in the body [4,5]. As such, IR-associated inflammation has garnered significant research interest as a potential therapeutic target for IR-associated diseases.

Existing studies have found that adipose tissue (AT), one of the target organs of insulin, is not only a storehouse of energy but also an active endocrine organ that can secrete a variety of bioactive molecules. Through this, AT participates in the metabolic processes of the body and alters insulin sensitivity locally and systemically [6]. AT consists of adipocytes and a stromal vascular fraction (SVF). The SVF is composed of endothelial cells, fibroblasts, and various immune cells such as macrophages, T cells, and B cells, thus underscoring its immunological and metabolic (immune metabolism) functions [6,7].

Adipose tissue macrophages (ATMs) make up the largest proportion of AT immune cells and are indispensable for maintaining their function. In the pathogenesis of obesity, IR, and T2DM, ATMs can increase their numbers by 5-10 fold through peripheral cell recruitment and local proliferation [8,9]. Accompanying these changes, the intrinsically highly malleable macrophages can alter their phenotype in

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response to cues from the local microenvironment, thereby altering their function [10]. As such, ATMs have become recognized to be key players in the development of inflammation and IR in AT [11] and form an important hub between immunity and metabolism.

In this review, we comprehensively investigate the relationship between ATMs, inflammation, and IR, with a focus on elucidating the regulatory factors associated with phenotypic changes in ATMs and the specific mechanisms mediating the development of IR in AT.

Origin and function of ATMs

In 1969, the classical model of the "mononuclear phagocyte system" was proposed. Based on the morphology, function, and origin of cells, promonocytes and their precursors in bone marrow, monocytes in peripheral blood, and macrophages in tissues were incorporated into the model [12]. In addition, a more primitive view has been formed of the origin of tissue macrophages, which are derived from circulating bone marrow-derived monocytes that migrate to tissues where they mature into macrophages, including Kupffer cells of the liver, alveolar macrophages, and ATMs [13]. Initially, tissue macrophages were regarded to be terminally differentiated cells, however, with later scientific advances and the availability of genetic fate mapping technologies, scientists gradually realized the importance of the yolk sac, an extra-embryonic hematopoietic site, for the generation of tissue macrophages. There, erythro-myeloid progenitors undergo a pro-macrophage differentiation stage to become macrophages [14,15]. Therefore, the current consensus is that macrophages can be broadly dichotomized into monocyte-derived macrophages and tissue-derived macrophages based on their origin [16].

In inflammatory states, tissue-produced chemokines attract circulating monocytes and induce their differentiation into macrophages, leading to their local infiltration. However, the dramatic increase in the number of tissue macrophages does not depend solely on this process. Local *in situ* proliferation of ATMs driven by monocyte chemotactic protein-1 (MCP-1) contributes significantly to the local accumulation of macrophages in AT [17]. As such, both monocyte infiltration and local macrophage proliferation play a crucial role in the accumulation of ATMs under inflammatory conditions.

Macrophages are functionally diverse and involved in physiological and pathological processes such as organism development, tissue repair, immunomodulation, and maintenance of homeostasis in the body [18]. The macrophage surface is littered with pattern recognition receptors that recognize the molecular programs expressed by microorganisms and damaged cells, namely pathogen-associated molecular patterns and damage-associated molecular patterns, respectively. Macrophages exhibit a prodigious capacity for phagocytosis, wrapping and engulfing invading pathogens and presenting them to adaptive immune response cells as part of the innate immune response [19,20]. Thereby, macrophages play an *in vivo* role in immune surveillance, immune defense, and immune self-stabilization.

In addition to pathogens, macrophages also use phagocytosis to remove senescent cells from the body, thereby enabling cellular self-renewal and regulation. These functions are preserved in the AT. The total number of adipocytes is determined during childhood and adolescence and is maintained within a relatively stable range in adulthood. Spalding *et al.* demonstrated that approximately 10 % of fat cells are renewed annually throughout adulthood, independent of the body mass index (BMI) [21]. Cell renewal is also active in AT and is characterized by the continuous removal and replacement of adipocytes. Macrophages play a key role in this process.

Necrotic adipocytes can recruit large numbers of macrophages to encircle them in crown-like structures (CLS) (Fig. 1). Having done this, macrophages then remove any dead adipocyte residue. The process of removing necrotic adipocytes by ATMs is thought to be a critical step in the repair and remodeling of AT [22]. In addition, recruited macrophages also secrete pro-inflammatory cytokines that mediate inflammation [23]. Thus, to some extent, the presence of CLS is considered to be one of the markers of a pro-inflammatory state in AT. To clarify the relationship between systemic IR and subcutaneous and visceral adipose inflammation, Bigornia *et al.* evaluated the CLS in AT as a marker of chronic inflammation and found a significant positive correlation between the presence of CLS and IR [24], indirectly confirming the important role of ATMs in IR.

In summary, ATMs are derived from the differentiation of yolk sac progenitor cells and the migration of circulating monocytes, which are essential for the immune regulation of the body. ATMs achieve self-renewal of AT through their powerful phagocytic capacity and maintain AT homeostasis by removing necrotic adipocytes to repair and remodel AT.

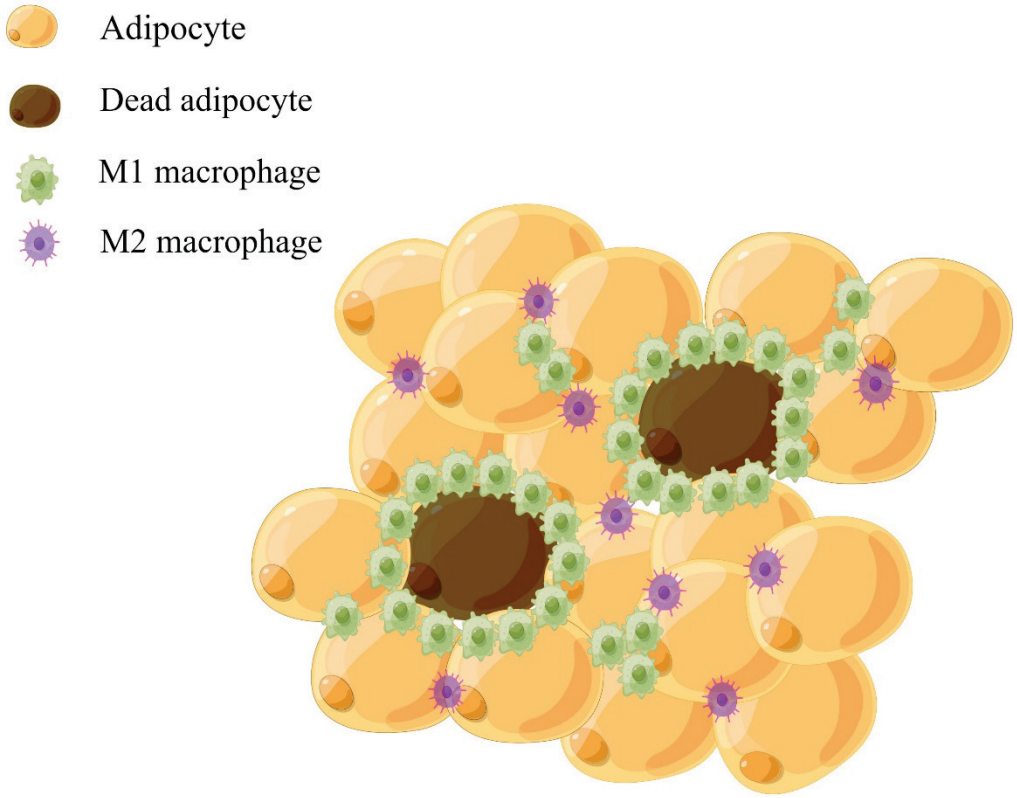

Fig. 1. "Crown-like structures (CLS)" in adipose tissue. Macrophages surround the necrotic adipocytes and form "CLS". During this process, recruited macrophages are predominantly of the M1 phenotype, and secrete a variety of pro-inflammatory factors. Therefore, "CLS" is considered as one of the hallmarks of adipose tissue inflammation.

ATM phenotypes

In response to the microenvironment, macrophages can rapidly adapt by increasing in numbers and altering their phenotype and function [25,26]. Classically, macrophages are dichotomously classified into activated M1 macrophages or alternatively-activated M2 macrophages. M1 macrophages are activated by interferon-γ (IFN-γ), lipopolysaccharide (LPS), and tumor necrosis factor (TNF) and have a high antigen-presenting capacity as well as high phagocytic and bactericidal functions. They release various pro-inflammatory cytokines such as interleukin-6 (IL-6), TNF-α, IL-12, reactive oxygen species (ROS), and nitric oxide (NO) that further activate inflammatory responses [27]. M2 macrophages can release multiple anti-inflammatory cytokines such as IL-10, transforming growth factor-β (TGF-β), and interleukin-1 receptor antagonist (IL-1ra) to suppress the inflammatory response and promote tissue repair [28,29]. M2 macrophages are further subdivided into four subtypes, M2a, M2b, M2c, and M2d, depending on external stimuli and their functions [30,31]. M2a (wound healing macrophages) are induced by interleukins (IL-4, IL-13), M2b (regulatory macrophages) are induced by exposure to immune complexes (ICs) and Toll-like receptor (TLR) ligands or agonists of IL-1R, M2c (acquired inactivated macrophages) are induced by IL-10, TGF-β, and glucocorticoids [32,33], and M2d (tumor-associated macrophages) are induced by TLR ligands and A2 adenosine receptor (A2R) agonists or IL-6 co-stimulation [34-36] (Fig. 2).

Transcriptional profiling has deepened our understanding of macrophage plasticity, showing that macrophage responses to stress signals involve complex cellular programs [37]. In the normal state, tissue macrophages predominantly exhibit the M2 subtype and help maintain the internal tissue homeostatic environment. However, in the inflammatory state, the phenotype of macrophages becomes altered. In the early stages of inflammation, M1 macrophages predominate while the late stages of inflammation are associated with the M2 macrophage phenotype [38]. In addition, in metabolic disease, ATMs present a complex phenotype that cannot be classified as M1 or M2; such cells are referred to as metabolically activated macrophages. These cells express lower levels of pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 than M1 macrophages,

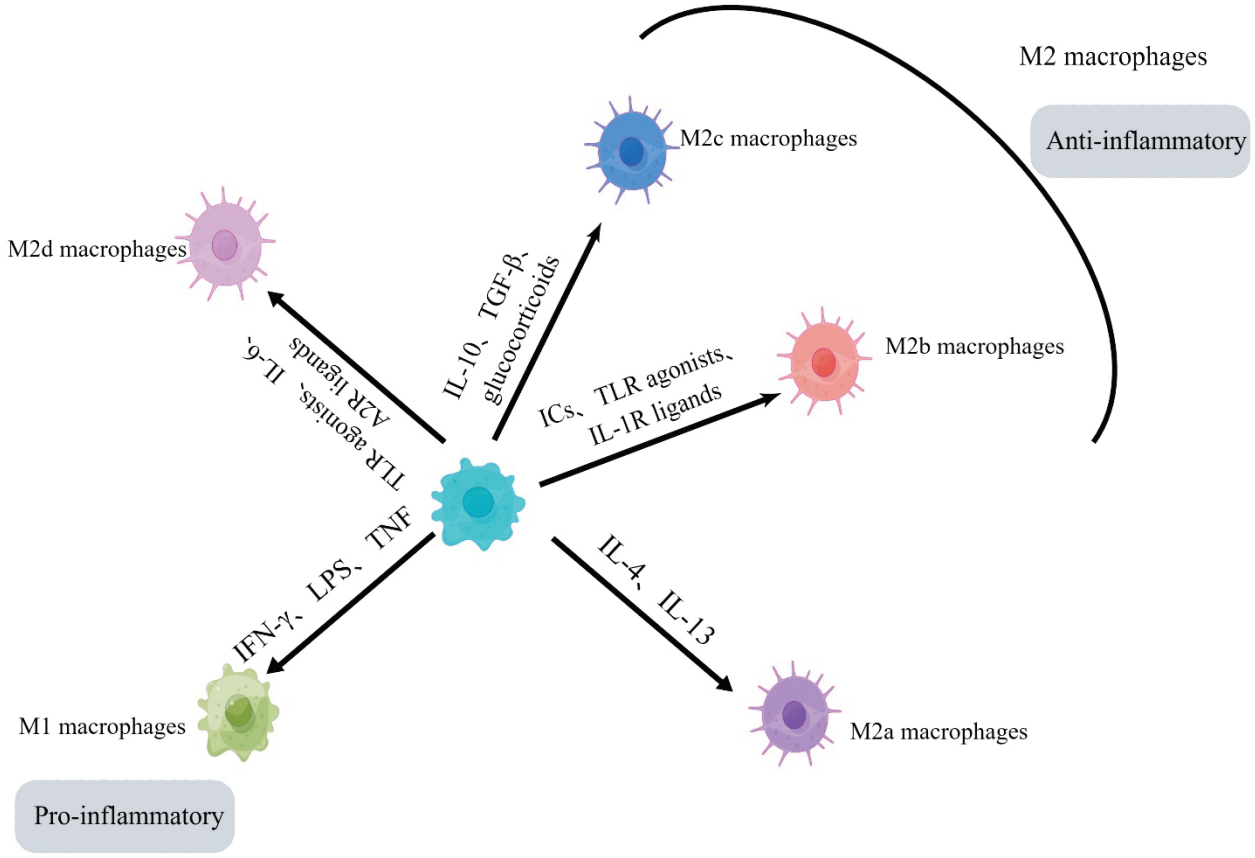

Fig. 2. Plasticity of macrophage phenotypes. Macrophages exhibit different phenotypes and perform their respective functions in response to different stimuli. M1 macrophages mainly show pro-inflammatory effects, whereas M2 macrophages (including M2a, 2b, 2c, and 2d) mainly show anti-inflammatory effects and promote tissue repair. IFN-γ = interferon-γ; LPS = lipopolysaccharide; TNF = tumor necrosis factor; IL = interleukin; TGF-β = transforming growth factor-β; ICs = immune complexes; TLR = Toll-like receptor; IL-1R = interleukin-1 receptor; A2R = A2 adenosine receptor.

and similarly low levels of CD206 as M2 macrophages. The emergence of the "metabolic activation" state is mainly associated with palmitate. On the one hand, palmitate binds to TLRs on the cell surface, driving the production of pro-inflammatory cytokines. On the other hand, palmitate is internalized by macrophages, activating p62 and PPARγ, thereby promoting lipid metabolism and suppressing inflammation. The balance between these two mechanisms determines the overall macrophage response to metabolic dysfunction [39,40]. Thus, it can be seen that macrophages can rapidly switch to unique phenotypes, based on microenvironmental cues, that facilitate the performance of diverse functions during the different stages of non-inflammatory and inflammatory conditions [41].

Factors regulating the ATM phenotypes

TLR4

Toll-like receptors (TLRs) are pattern recognition receptors that trigger the activation of pro-inflammatory signaling pathways such as NF-κB, leading to the release of inflammatory molecules such as cytokines and chemokines. Each TLR plays a unique and critical role in innate immunity [42-44]. TLR4 stands at the cross-roads of nutrition, lipids, and immunity. TLR4 is a major endogenous receptor for LPS [45]; LPS is also an important stimulant of the M1 macrophage phenotype. As such, TLR4 may regulate the ATM phenotype. TLR4 mRNA was shown to be significantly elevated in the AT of obese mice. This study also pointed out that the TLR4 signaling pathway also mediates the process of free fatty acid-induced macrophage inflammation [46]. A significant increase in TLR4 mRNA expression has also been observed in the visceral fat of obese patients [47].

Exercise training has been shown to modulate the ATM phenotype in obese mice, and may inhibit inflammation in AT by downregulating TLRs [48]. Shan *et al.* showed that TLR4 signaling in perivascular stromal cells is an important mediator of pro-inflammatory macrophage accumulation in white adipose tissue (WAT)

[49]. By constructing a TLR4-specific knockout mouse model, Orr *et al*. found that TLR4 deficiency promotes the polarization of ATMs toward the M2 phenotype and thereby promotes the activation of alternative macrophages and reduces inflammation in AT [50]. In addition, Griffin and colleagues found that a high-fat diet affects macrophage proliferation and polarization by enhancing TLR4 expression in AT and its downstream signaling [51]. In conclusion, the aforementioned studies suggest that TLR4 signaling plays an important role in the local proliferation and phenotypic transformation of ATMs.

ROS

The redox status in the body significantly affects the macrophage phenotype. Reactive oxygen species (ROS), a direct product of oxidative stress, have been shown to promote the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and other inflammatory responses in macrophages and are important mediators of pro-inflammatory signaling pathways [52]. Free fatty acids (FFA), which regulate M1 polarization *in vitro*, are closely associated with increased ROS production and macrophage recruitment [53]. However, several studies have reported inconsistent effects of ROS on the macrophage phenotype. In the presence of high glucose, ROS promotes M1 macrophage polarization by impairing the autophagy-lysosome system [54]. Acin-Perez *et al.* found that the ROS scavenger NAC significantly increased the proportion of M1 macrophages in WAT, showing that ROS promotes M1 polarization [55]. Others have demonstrated that oleanolic acid, a natural triterpenoid, inhibits the activation of the NLRP3 inflammasome by reducing ROS production, thereby inhibiting M1 polarization and improving adipose chronic inflammation and IR [56]. However, Wang *et al.* characterized a near-infrared fluorophore (IR-61) that preferentially accumulates in ATMs and demonstrated that it enhances the content and activity of the mitochondrial complex of ATMs *via* the ROS-Akt-Acly pathway, thereby inhibiting M1 macrophage activation [57]. Thus, ROS plays an important role in regulating the phenotypic transformation of macrophages, but its specific contextual mechanisms of action still need to be explored in more depth.

ROS includes superoxide, hydrogen peroxide, and hydroxyl radicals, and its sources are mitochondria, NADPH oxidase, peroxisomes, and the endoplasmic reticulum [58]. Among them, mitochondria, as the main sites of biological oxidation and energy conversion, are the main sources of ROS production [59]. Mitochondrial ROS impacts the metabolic processes of proteins, lipids, glucose, and other energetic substances [60]. It has been widely demonstrated that changes in lipid metabolism play an important role in regulating the phenotypic transformation of ATMs. Macrophages in the AT of lean animals mostly exhibit the M2 subtype. In contrast, in obese animals, ATMs are mostly of the M1 subtype [61]. Lumeng *et al.* isolated SVF from excised epididymal fat pads of male mice fed a normal diet and a high-fat diet and found that diet-induced obesity resulted in the conversion of ATMs from the M2 subtype to the M1 subtype [62]. In obese states, the reduced lipid storage efficiency of WAT and the release of lipids from adipocytes create a lipid-rich microenvironment for ATMs. In addition, the expression of very low-density lipoprotein receptors (VLDLR) is increased in obese ATMs. Activation of these receptors by VLDL causes an increase in intracellular triglyceride levels, ultimately leading to the polarization of ATMs toward the M1 pro-inflammatory subtype, leading to the development of IR [63].

KLF4

Kruppel-like factors (KLFs) are a subfamily of zinc finger-like DNA-binding transcriptional regulators involved in cell growth, proliferation, and differentiation [64,65]. KLF4 was isolated from the NIH 3T3 library and named the intestinal enrichment Kruppel-like factor, a well-studied member of the KLF family. Ectopic expression of KLF4 induces macrophage maturation. In addition, KLF4 has been shown to mediate IL-4-induced M2 macrophage polarization and inhibit inflammatory signaling. KLF4 regulates key signaling pathways that control macrophage activation and regulates the macrophage phenotype [66].

Obese patients have been found to express 50 % less KLF4 in AT than lean patients; a similar phenomenon was found in isolated SVF. In addition, this study also evaluated the expression of M1 and M2 macrophages marker genes in SVF of wild mice fed a high-fat diet and myeloid KLF4 knockout mice, finding that KLF4 is a novel regulator of macrophage polarization and that its deficiency may affect the ATM phenotype [67]. There was a significant negative correlation between miR-34a and KLF4 mRNA expression in adipocyte-secreted exosomes. miR-34a inhibited the polarization of ATMs to the M2 subtype by suppressing KLF4 expression, and

conversely, KLF4 overexpression significantly decreased the expression of M1 macrophage markers and enhanced the expression of M2 macrophage markers [68]. In addition, transfection of bone marrow-derived macrophages using miR375 inhibitors confirmed that the effect of miR375 on macrophage polarization was at least partially mediated by KLF4 [69]. Using a high-fat diet-induced IR model, Luan *et al.* verified that macrophage cyclic-AMP response binding protein (CREB) promotes macrophage polarization towards the M2 subtype by upregulating KLF4, thereby protecting AT from IR in the context of obesity [70]. These studies highlight the importance of KLF4 as an important regulatory molecule for the polarization of ATMs.

PPARγ

The transcription factor peroxisome proliferator-activated receptor-γ (PPARγ) belongs to the family of ligand-dependent nuclear receptors and is the target of action of the insulin sensitizer thiazolidinedione drugs for the treatment of T2DM [71]. In 1998, PPARγ was found to be expressed in macrophages and scholars have since worked to better understand its role in macrophage activation and metabolism [72]. PPARγ has now been confirmed to be involved in the differentiation, infiltration, and polarization of macrophages and to play a critical role in the IL-4 stimulation of macrophages [73]. IL-4 was found to induce the expression of surface markers of alternatively activated macrophages in a PPARγ-dependent manner and that deletion of the PPARγ gene in macrophages increases M1-subtype ATM cells and IR in AT [74,75].

The combined effect of PPARγ and its ligand rosiglitazone significantly enhanced the ability of IL-4 to activate the arginase I promoter, suggesting that PPARγ is directly involved in the regulation of macrophage activation [75]. Previous studies found that PPARγ expression is significantly lower in the AT of mice fed a high-fat diet compared to mice fed a regular diet. A high-fat diet leads to the recruitment of more M1 macrophages, in part by downregulating PPARγ, thereby maintaining a chronic inflammatory state in AT during obesity [76]. PPARγ is a key regulator of alternative macrophage polarization and interferon regulatory factor 6 (IRF6) was shown to inhibit M2 macrophage polarization by directly downregulating PPARγ expression in macrophages; the effect of the IRF6/PPARγ regulatory axis on the ATM phenotype provides a theoretical basis for the study of metabolism and immune regulation in obese AT [77]. Furthermore, recent evidence suggests that PPARγ expression is significantly decreased in the epididymal AT of high-fat fed C57BL/6J obese mice and that ginsenoside compound K improves IR by upregulating PPARγ expression, regulating macrophage polarization, and reducing the release of inflammatory factors [78]. These findings suggest that PPARγ modulation of the ATM phenotype is a potentially important target for improving IR, which is mainly characterized by chronic low-grade inflammation.

In brief, macrophage phenotypes are susceptible to regulation by the local microenvironment. TLR4, ROS, KLF4, and PPARγ have been repeatedly shown to be involved in the phenotypic regulation of ATMs. Among these, TLR4 mediates the polarization of ATMs to the M1 subtype, which also regulates the local proliferation of macrophages. KLF4 and PPARγ regulate the polarization of ATMs to the M2 subtype, reduce the release of pro-inflammatory factors, and improve IR. How ROS affects the macrophage phenotype and the underlying mechanisms of action are not yet fully understood.

Mechanisms of ATM-mediated insulin resistance

Insulin signaling pathway

Insulin binds to cell surface insulin receptors and subsequently activates tyrosine kinase, which further causes phosphorylation of insulin receptor substrate (IRS). The phosphorylation of key tyrosine residues of IRS exposes the binding site, which is recognized and bound by phosphatidylinositol 3 kinase (PI3K). PI3K then phosphorylates PIP2 to PIP3, which binds to AKT and 3-phosphoinositide-dependent protein kinase-1 (PDK1), prompting PDK1 to phosphorylate the AKT protein leading to AKT activation [79,80]. Akt activation regulates intracellular glucose transporter 4 (GLUT4) translocation to the plasma membrane, mediating the transport of glucose [81,82]. In AT, activation of the PI3K/Akt signaling pathway also inhibits phosphodiesterase 3B (PDE3B), protein phosphatase 1 (PP1), and protein phosphatase 2A (PP2A) and inhibits lipolysis, which in turn inhibits hepatic gluconeogenesis [83] (Fig. 3).

M1 ATMs promote insulin resistance

The altered insulin sensitivity in AT is closely related to the macrophage phenotype; the conversion of macrophages from an M2 anti-inflammatory phenotype to an M1 pro-inflammatory phenotype is thought to be

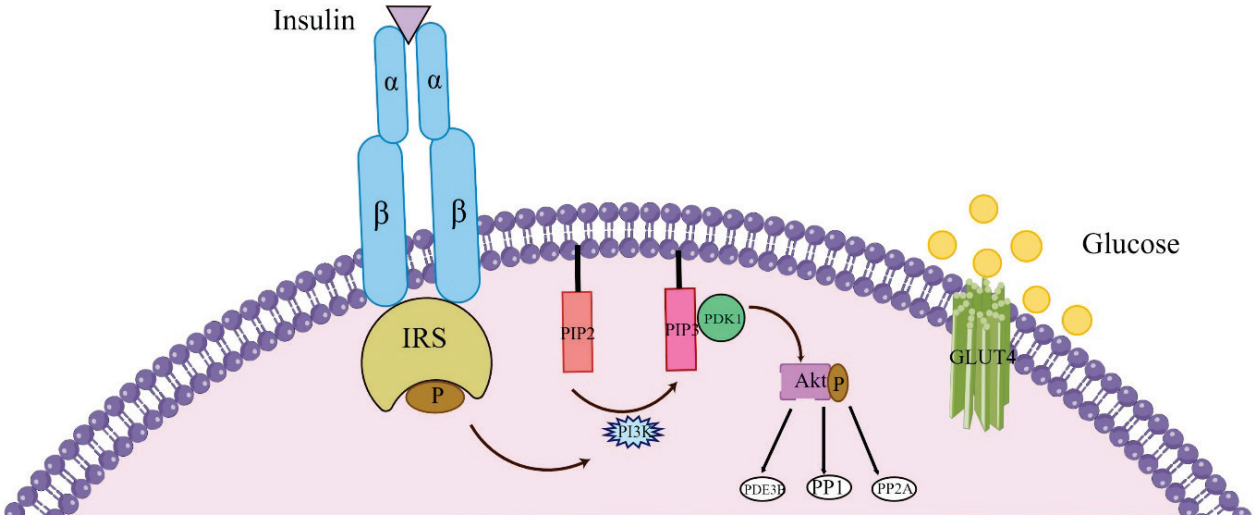

Fig. 3. Insulin signaling pathway. The binding of insulin to the receptor causes phosphorylation of insulin receptor substrate(IRS), after which the catalytic activity of PI3K is activated, leading to the activation of Akt, which mediates glucose transport through glucose transporter 4 (GLUT4). Meanwhile, activated Akt continues to activate downstream signaling pathways to regulate glucose homeostasis. It is worth mentioning that in adipose tissue, the inhibition of lipolysis and gluconeogenesis by insulin may be associated with phosphodiesterase 3B (PDE3B), protein phosphatase 1 (PP1), and protein phosphatase 2A (PP2A). IRS = insulin receptor substrate; PI3K = phosphatidylinositol 3 kinase; PIP2 = phosphatidylinositol 4,5-bisphosphate; PIP3 = phosphatidylinositol 3,4,5-trisphosphate; PDK1 = phosphoinositide-dependent protein kinase 1; PDE3B = phosphodiesterase 3B; PP1 = protein phosphatase 1; PP2A = protein phosphatase 2A; GLUT4 = glucose transporter 4.

the main cause of reduced insulin sensitivity [84]. The process of macrophage-mediated IR is a "double whammy". First, there is an activation of tissue macrophages; in this case, we refer specifically to the activation of ATMs which release pro-inflammatory cytokines. Second, there is an activation of inflammatory signaling pathways within neighboring insulin target cells (adipocytes), leading to the development of IR [85]. Various pro-inflammatory cytokines such as TNF-α and IL-6 produced by M1 ATMs can be directly involved in the development of IR, and the activation of inflammatory signaling can enhance the effects of IR.

TNF-α

Using the glucose tolerance test as an index to evaluate insulin sensitivity, Kern *et al.* found a significant positive correlation between the levels of TNF-α and IR severity [86]. TNF-α reduces the expression of GLUT4, the most abundant glucose transporter protein in adipocytes, which can directly affect the insulin-regulated glucose transport process [87]. TNF-α can also promote the accumulation of ceramide by activating the activity of sphingomyelinase that catalyzes the hydrolysis of sphingolipids to ceramide, which is thought to be an important mediator linking TNF-α to IR. In addition, TNF-α has been shown to reduce the levels of adiponectin (ADPN) *in vitro* [88], which is the most abundant adipocytokine in plasma and has a direct positive effect on tissue insulin sensitivity. On the other hand, ADPN has also been found to indirectly affect tissue insulin sensitivity by promoting exosome secretion, which leads to a decrease in ceramide production [89]. In addition, TNF-α impairs insulin sensitivity in AT by inducing serinephosphorylation of insulin receptor substrate-1 (IRS-1), a key substrate for insulin signaling. Activated IRS-1 binds to PI3K and activates downstream signaling; once some sites (such as serine 307) of IRS-1 are phosphorylated, insulin signaling is diminished [90].

IL-6

ATMs are a major source of IL-6 in AT. IL-6 is a pro-inflammatory cytokine that is closely associated with the development of inflammation and IR. Elevated IL-6 levels independently predict T2DM [91]. IL-6 has been shown to induce IR through multiple pathways. Chronically elevated IL-6 induces the expression of suppressor of cytokine signaling 3 (SOCS 3); its overexpression impairs downstream signaling by inhibiting tyrosine phosphorylation of IRS proteins, thereby causing IR [92]. Like TNF-α, IL-6 represses the gene transcription of IRS-1 and GLUT4, and the reduced expression of these genes and proteins directly leads to impaired insulin signaling and an imbalance of glucose homeostasis [88,93]. IL-6 has also been shown to negatively correlate with ADPN levels; following co-incubation of AT with IL-6 and the soluble receptor,

ADPN mRNA expression was significantly reduced [94]. However, several studies have shown that IL-6 does not exclusively act as a negative regulator of insulin signaling. Stanford *et al.* found that elevated circulating IL-6 increased energy expenditure, reduced obesity, and improved systemic glucose metabolism [95], which is consistent with previous findings [96]. Currently, the controversial relationship between IL-6 and IR and glucose metabolism can be explained partly by the response time of IL-6. Chronic elevation of IL-6 leads to the development of IR and, conversely, acute elevation of IL-6 enhances insulin sensitivity [91]. The specific mechanisms involved in IL-6 regulation of insulin sensitivity in AT need to be further clarified.

In short, M1 macrophages can secrete pro-inflammatory factors such as TNF-α and IL-6 leading to the development of IR. TNF-α can eventually cause IR by reducing the expression of GLUT4 and adiponectin, increasing the level of ceramide, and inducing IRS-1 serine phosphorylation. IL-6 has similar effects, and can also indirectly inhibit the tyrosine phosphorylation of IRS proteins leading to IR by inducing the expression of SOCS-3. The role of IL-6 in regulating insulin sensitivity in AT remains controversial.

Conclusions

The specific mechanisms of IR in AT remain incompletely understood. There is increasing evidence that chronic inflammation plays an important role in the development of IR. At the same time, the role of tissue-resident immune cells in inflammation and IR cannot be ignored. The relationship between ATMs, as the most abundant immune cells in AT, and IR has been widely explored. The most studied of these involve the phenotypic changes of ATMs. The regulatory factors of the ATM phenotypes and the specific mechanisms through which ATMs mediate IR in AT are ongoing topics of research. Modulation of the ATM phenotype by various technical means may ultimately allow us to improve the treatment of inflammation and IR in AT.

Conflict of Interest

There is no conflict of interest.

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