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The role of macrophage and adipocyte mitochondrial dysfunction in the pathogenesis of obesity

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Obesity has emerged as a prominent global public health concern, leading to the development of numerous metabolic disorders such as cardiovascular diseases, type–2 diabetes mellitus (T2DM), sleep apnea and several system diseases. It is widely recognized that obesity is characterized by a state of inflammation, with immune cells-particularly macrophages-playing a significant role in its pathogenesis through the production of inflammatory cytokines and activation of corresponding pathways. In addition to their immune functions, macrophages have also been implicated in lipogenesis. Additionally, the mitochondrial disorders existed in macrophages commonly, leading to decreased heat production. Meantime, adipocytes have mitochondrial dysfunction and damage which affect thermogenesis and insulin resistance. Therefore, enhancing our comprehension of the role of macrophages and mitochondrial dysfunction in both macrophages and adipose tissue will facilitate the identification of potential therapeutic targets for addressing this condition.

KEYWORDS

macrophages, mitochondrial disorder, adipose tissue, obesity, pathogenesis

1 Introduction

Obesity is a chronic metabolic disease whose main characteristic is harmful overweight and the accumulation of adipose tissue (AT). The WHO definition of obesity is a BMI≥30 kg/m^2 (1). For several decades, the prevalence of obesity has increased significantly. According to a recent study published in *Lancet*, there were 159 million obese children and adolescents, and 879 million obese adults globally in 2022. The global obesity rate for children and adolescents in 2022 was approximately four times greater than that in 1990. Among adults, obesity rates have nearly tripled in males and more than doubled in women (2). Frequently, obesity is related to a variety of metabolic diseases, such as insulin

resistance-induced type 2 diabetes and cardiovascular disease (CVD) (3, 4). Compared with healthy individuals, obese individuals have a greater hazard ratio for cancers of the breast, kidney, pancreas, and esophagus (5, 6). Moreover, childhood obesity is closely correlated with metabolic diseases in adulthood, so prevention of childhood obesity is essential (7).

The basic cause of obesity is an imbalance between caloric intake and consumption; this situation is usually caused by an excess high-fat diet and a lack of physical activity (8). Therefore, common individual management strategies for the prevention of obesity include reducing the consumption of high-carbohydrate or high-fat diets and increasing the frequency of workouts. By doing so, a weight loss of 5% to 7% can be produced on average, which is not desirable or sufficient (9). Under conditions of obesity, several alterations occur, including metabolic pathways activation related with energy metabolism, proinflammatory cytokine upregulation, immune cell population changes, and mitochondrial dysfunction (10–13). Currently, various anti-obesity medications target these alterations to control energy balance and inhibit inflammation, thus achieving the goal of weight loss and reducing the corresponding disease risks (14).

As the most abundant immune cell type in adipose tissue, macrophages play crucial roles in maintaining adipose homeostasis and regulating the immune system (15). Not only the number but also the tissue localization and phenotype of macrophages are largely altered during the process of obesity (12). Macrophages in adipose tissue are the principal source of inflammatory mediators which contribute largely to the production of chronic low-grade inflammation in obese individuals (16, 17). In addition to their immune functions, macrophages have also been implicated in lipogenesis. Additionally, mitochondrial disorders commonly exist in macrophages, leading to decreased heat production in adipose tissue. Moreover, adipocytes exhibit mitochondrial dysfunction and damage, which affect thermogenesis and insulin resistance. Mitochondrial disorders can act as a bridge that connects macrophages and adipocytes, together contributing to the development of obesity. In this review, we summarize both macrophages and adipose tissue mitochondrial disorders in adipose tissue.

2 Overview of obesity-associated factors

Obesity is the result of energy input being greater than energy output, and then excess energy is converted into fat under the subcutaneous or internal organs. The factors that induce obesity can be divided into congenital factors, postnatal factors, and environmental factors. Congenital factors mainly refer to related gene expression. During the process of evolution, those who could store and utilize energy more effectively and tolerate hunger for longer may have a comparative reproduction advantage over those who do not have these properties according to survival and selection stress, thus resulting in overrepresentation of genetic variants that are beneficial for faster eating, excess energy absorption and storage in adipose tissue (18).

Many studies have investigated genes associated with obesity. For example, fat mass and obesity-associated genes (FTOs) were identified as obesity markers by genome-wide association studies, and FTO knockout mice exhibited weight loss (19). Additionally, with the help of whole-exome sequencing, a series of genes were identified as BMI-related genes. For example, G-protein coupled receptor (GPR75) was associated with a lower BMI, whereas calcitonin receptor (CALCR) was correlated with a higher BMI (20). Other sequencing analyses focusing on sex and age differences also revealed that several genes function in men and women or adults and children separately (21). Moreover, mutations in genes encoding adipose tissue hormones and hormone receptors play a significant role in the development of obesity (22–25). Findings related to these genes not only help explain the probable mechanism of obesity occurrence but also offer potential therapeutic targets for obesity.

Excessive food intake, unhealthy eating habits, insufficient physical activity, a lack of sleep, psychological and emotional changes, region and socioeconomic status are all influencing factors of overweight (8, 26–28). In addition to these factors, immune and metabolic status are critical propellants in promoting obesity because adipose tissue is not only an energy bank but also an endocrine organ (29). Innate immune cells, including macrophages, lymphocytes, dendritic cells, neutrophils, eosinophils and natural killer cells, which reside in adipose tissue can secrete numerous cytokines that affect metabolic pathways and facilitate inflammation (16, 30–33).

3 Adipose tissue macrophages

Obesity is actually a state of chronic inflammation, and the infiltration and recruitment of adipose tissue macrophages (ATMs) greatly contribute to the process of obesity. Macrophages are a group of cells that are differentiated from monocytes and have the ability to phagocytose cell debris and pathogens. Generally, there are two principal macrophage populations. The classically activated status is type 1 macrophages (M1 macrophages), which usually express CD11c, TNF, IL-6, IL-1β, and Nos2. They are commonly activated by IFN-γ, LPS and GM-CSF, and secrete proinflammatory cytokines (34–36). The alternatively activated type is type 2 macrophages (M2 macrophages), which express arginase 1(Arg1), CD206, and CD301 (37). M2 macrophages are usually stimulated by M-CSF, IL-13 and TGF-β, and they secrete anti-inflammatory cytokines, including IL-1RA and IL-10 (38). M2 macrophages can be divided into four subtypes according to different stimuli and cell markers. M2a cells, also called alternative activated cells, can be activated by IL-4 and IL-13 and they highly express CD206, CD209 and FIZZ1. Type II alternatively activated cells, commonly called M2b cells, are usually activated by IL-1β or LPS and they highly express CD80 and CD14. M2c macrophages are also referring to acquired deactivated cells; they can be stimulated by TGF-β and IL-10 and highly express CD163 and CD206. M2d macrophages, also called tumor-associated macrophages (TAMs), are induced by TLR agonists, and they may participate in the proliferation and invasion of tumor cells (38–40). In fact, the number, phenotype, and tissue

localization of macrophages can be significantly altered as BMI increases.

In addition to the two classic cell subtypes, other macrophage subtypes are also associated with adipose tissue. In a previous study, $CD11c^{-}CD206^{-}$ ATMs were recognized as type 3 macrophages, which localize to crown-like structures (CLSs) and express pro-inflammatory cytokines (41, 42). $CD11c^{+}CD206^{+}$ ATMs are in the middle state of M1/M2 ATMs, which have relatively high levels of lipid-rich vacuolar and mitochondrial RNAs, as well as transcripts encoding APOE, FABP4, and fatty acid metabolism enzymes (43). 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) is a reductase which catalyzes inactive glucocorticoids into active form (44). One study revealed that the 11β-hydroxysteroid dehydrogenase type 1–glucocorticoid receptor (11β-HSD1-GR) regulatory axis plays an important role in the process of switching to the M1/M2 phenotype and prevention of this process may be a potential therapeutic target for obesity (45).

Lipid-associated macrophages (LAMs) are a subtype of $CD11c^{+}CD206^{+}$ ATMs. LAMs express a series of transcriptional genes associated with lipid embolism and phagocytosis, including Trem2, Lipa, and Ctsb. In particular, Trem2, which is highly expressed in LAM, plays a crucial role in ATM remodeling, prevention of adipocyte hypertrophy and maintenance of metabolic homeostasis (46). Another subtype of lipid-laden macrophages named $CD9^{+}$ macrophages, which localize to CLSs, express several genes related to lysosomal pathways and proinflammatory mediators (47).

Additionally, a metabolically activated macrophage (MMe) phenotype, which overexpresses ABCA1, CD36 and PLIN2 but does not express M1 cell surface markers including CD38, CD319 and CD274, and M2 cell surface markers including CD163 and CD206, is produced under stimulation with saturated free fatty acids (FFAs) (48). (Table 1) Excessive lipids can polarize macrophages toward an inflammatory state and induce lysosome biogenesis in macrophages, which helps lipid clearance. The inhibition of ATM lysosomal activity inhibits lipid metabolism, increases lipid accumulation in ATMs, and decreases overall AT lipolysis (49). Dead adipocytes are a plentiful source of FFAs, which are essential for metabolic activation, and MMe can clear these dead cells through lysosomal exocytosis with the help of TLR2, NOX2, and MYD88 (50) (Figure 1).

TABLE 1 Macrophages subtypes related with obesity.

Type of macrophages	Cell marker	Function	Reference
Lipid-associated macrophages (LAM)	Trem2, Lipa, Ctsb	ATM remodeling	(46)
$CD9^{+}$	CD9	Related with lysosomal pathways and proinflammatory mediators	(47)
metabolically activated macrophage (MMe)	ABCA1, CD36, PLIN2	clear dead cells through lysosomal exocytosis	(48)

4 Regulatory factors governing macrophage polarization

Macrophage polarization is crucial for inflammation and obesity. There are various regulatory factors governing macrophage polarization.

As one of the most important inducers of M1 polarization, LPS stimulation increases the expression of M1 macrophage markers, such as toll-like receptor 4 (TLR4), CD36, and CD68 (51). It can interact with TLR4, together inducing production of TRIF, TRAM and Myd88, and the former two can recruit TANK through tumor necrosis factor receptor-associated factor 3 (TRAF3), then activate and combine with TANK-binding kinase 1 (TBK1), thus activating interferon-regulatory factor 3(IRF3), while Myd88 activates NF-κB pathway (52). Additionally, IFN-γ secreted from Th1 cells, NK cells and $CD8^{+}$ T cells can activate Janus kinase 1(JAK1) and Janus kinase 2 (JAK2), consequently leading to the activation of signal transducer and activator of transcription 1(STAT1), which together promote M1 polarization (53). Similarly, GM-CSF contributes to M1 polarization through JAK2-STAT5 signaling pathway (54). Except these molecules, hormones also participate in the process. For example, Leptin is a protein encoded by ob genes which is generally thought to be a proinflammatory cytokine (55). Leptin/obR significantly activated M1 macrophages via JNK/STAT3/AKT signaling and CXCL2 production (56). Usually, obesity leads to an increase in proinflammatory T cells, including $CD4^{+}$ Th1 and $CD8^{+}$ effector T cells, whereas anti-inflammatory Th2 cells decrease in adipose tissue, which induces macrophage polarization toward the M1 phenotype (57). And leptin can influence the polarization of $CD4^{+}$ T cells toward the Th1 phenotype by enhancing Th1 responses and suppressing Th2 immunological responses (58). Importantly, diet-induced obesity increases the number of NK cells and causes them to release IFN-γ and TNF-α in visceral adipose tissue, amplifying polarization and infiltration of M1 macrophage (59).

Correspondingly, there are a series of factors involved in M2 polarization. IL-10 promotes gene expression associated with an M2-like phenotype, and this process was determined to be STAT3 dependent through JAK1 activation (60, 61). IL-3 can activate JAK2 followed by STAT5 recruitment, leading to M2 polarization (62, 63). The binding of IL-4 and IL-13 to the corresponding receptor activates STAT6 through JAK1 and JAK3, finally activates IRF4 causing macrophages to undergo M2 polarization (64). Besides, adiponectin, a 247 amino acid protein, mainly plays a role in metabolism control by promoting glycolysis and fatty acid oxidation while inhibiting gluconeogenesis (65). It can regulate M2 macrophage polarization through activating the jumonji domain-containing - 3 (JMJD3)-IRF4 axis (66). Furthermore, adiponectin can affect the secretory function of macrophages, which is demonstrated by reduced secretion of proinflammatory cytokines such as IL-6 and TNF from macrophages and increased

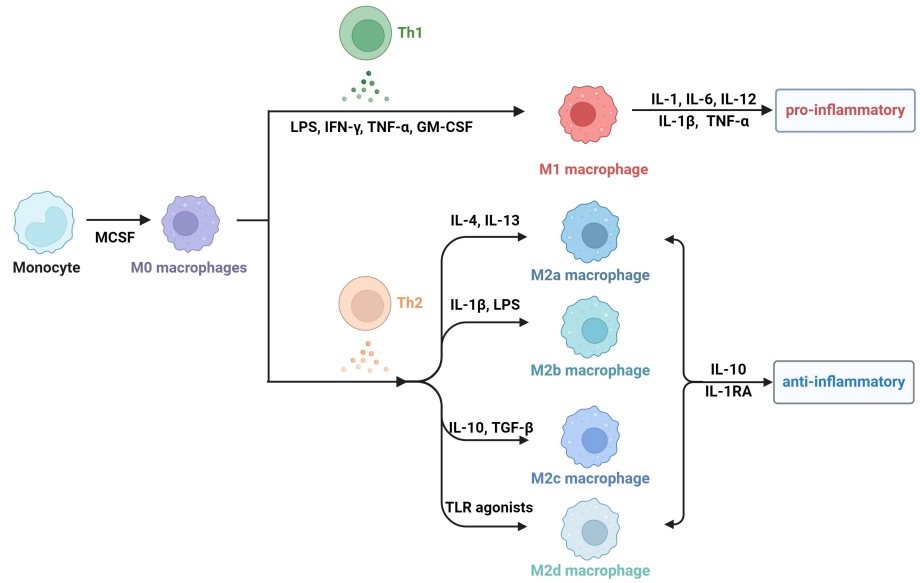

FIGURE 1
The subtype classification of macrophages.

production of anti-inflammatory cytokines, including IL-10 and IL-1RA (67).

Besides, IRF6 reduces M2 polarization by binding to the peroxisome proliferator-activated receptor γ (PPARγ) promoter and limiting its expression, while the JAK1/3-STAT6 pathway can inhibit IRF6 expression (68). Signal regulatory protein α (SIRPα) has been demonstrated to promote M2 polarization, whereas the Notch pathway can activate M1 polarization through the suppression of SIRPα expression (69). There also exists a phosphoenolpyruvate carboxykinase 2(PCK2)- AMP-activated protein kinase (AMPK)- mammalian target of rapamycin(mTOR) pathway regulating M2 polarization (70). AMPKα1 and AMPKβ1 are both important for M2 polarization, and AMPKβ1 deletion in macrophages decreases the mitochondrial content and rate of FAO (71, 72). (Figure 2)

Overall, inhibiting factors polarizing macrophages toward M1 and facilitating factors polarizing macrophages toward M2 can be therapy targets for obesity.

5 Regulatory factors governing macrophage recruitment

Macrophage recruitment plays a crucial role in promoting obesity and related inflammation. Compared with lean mice, obese mice exhibit increased infiltration of macrophages, accounting for 40% of all AT cells in obese mice (73). 90% of the macrophages that infiltrate the adipose tissue of obese humans and animals create characteristic CLSs surrounding dead adipocytes (74). Saturated fatty acids released by adipocytes and proinflammatory cytokines such as MCP-1 and TNF-α secreted from macrophages can lead to macrophage recruitment (75). Together, these factors augment inflammation in obesity and increase insulin resistance.

Monocyte chemoattractant protein-1 (MCP-1) is a proinflammatory chemokine that is produced largely by macrophages and endothelial cells (76). C-C motif chemokine receptor-2 (CCR2) is the receptor of MCP-1 (also called CCL2). The main function of MCP-1/CCR2 is regulating monocyte and macrophage recruitment. MCP-1 levels in plasma increased in both genetically obese diabetic (db/db) and WT mice with obesity caused by a high-fat diet, leading to macrophage infiltration. Conversely, MCP-1 gene knockout reduces macrophage accumulation in adipose tissue (77). Therefore, inhibiting the expression of MCP-1, CCR2, or other factors that can regulate the levels of MCP-1 may provide potential therapeutic methods for obesity.

Other chemokines, such as C-X-C motif receptor 3 (CXCR3) and C-X-C motif chemokine receptor 7 (CXCR7), are involved in the recruitment of macrophages to adipose tissue. In Th1 cells, CXCR3 combines with its ligands CXCL9 and CXCL10 to produce memory and effector T cells (78). Mice fed a high-fat diet presented increased numbers of CXCR3-expressing $CD8^+$ T cells and IFN-γ-expressing $CD4^+$ T cells. These cells attract and polarize macrophages toward an M1 response, leading to chronic low-grade inflammation during obesity (79). $CXCR3^{-/-}$ mice presented a decreased VAT macrophage response, and $CXCR3^{-/-}$ macrophages presented a defective response to LPS, resulting in a reduction in IL-12 and TNF-α synthesis *in vitro* (80). Therefore, targeting the CXCR3 receptor may be a potential treatment for obesity. Additionally, CXCR7 is expressed in adipose tissue, and its ligands CXCL11 and CXCL12 mediate macrophage chemotaxis and

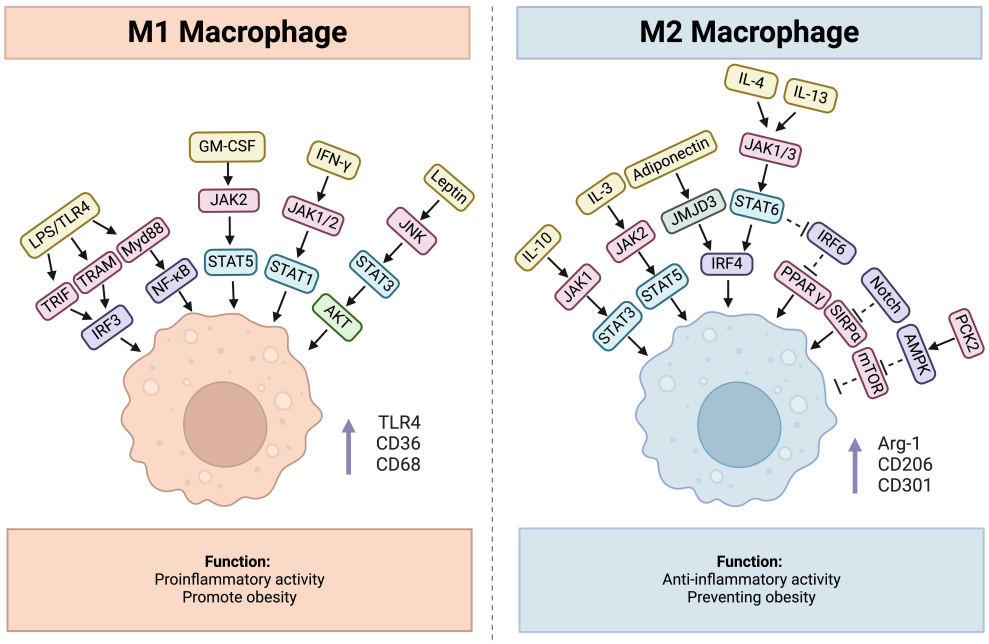

FIGURE 2
Factors influencing process of macrophage polarization, cytokines, hormones, and related signaling pathways are included.

phagocytosis and contribute to inflammation during obesity (81, 82). In obesity, the expression of CXCR7, CXCL11 and CXCL12 is increased, and CXCR7 neutralizing therapy with an anti-CXCR7 antibody can not only reduce macrophage infiltration and inflammation in obesity but also improve insulin resistance (83).

6 ATMs influence lipid metabolism and the energy state

The main function of adipose tissue is energy storage, and adipose tissue is divided into white adipose tissue (WAT) and brown adipose tissue (BAT). WAT, including subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), plays an important role in storing excessive lipids as triglycerides and releasing free fatty acids (FFAs) in the state of hunger. In contrast, BAT is rich in mitochondria, which can divert ATP into heat through uncoupling protein 1 (UCP1) and uncoupling electron transport to maintain temperature balance and fight against obesity (84). In fact, beige adipose tissue, similar to BAT, has heat production ability (85). Since the energy consumption of BAT and beige adipose tissue is greater than that of WAT, increasing the percentage or promoting the browning process of BAT and beige adipose tissue may be a potential therapy to combat obesity. For example, succinate is an intermediate metabolite of the tricarboxylic acid cycle that plays an indispensable role in energy production via the mitochondrial pathway. The increasing circulating level of succinate in BAT and beige fat increases whole-body energy expenditure, exacerbates obesity and inhibits systemic tissue inflammation. Mechanistically, succinate affects BAT mitochondrial or mitochondria-related proteins, which can help promote body weight loss (86). However, adipocyte disorders occur in obesity, and adipocytes lose their heat production ability, resulting in the accumulation of dead adipocytes. The clearance of these dead cells requires macrophages.

In fact, macrophages function as important members of intrinsic immunity and can influence metabolic pathways and metabolites in adipose tissue. One of the most significant features of macrophages in obesity is the upregulation of lysosome-related pathways. A previous study revealed that the surface marker LAMP-1, which indicates lysosome exocytosis, is increased in CLS macrophages (50). In addition, macrophages can absorb fat from dead adipocytes through an acidified interface between adipocytes and macrophages. If lysosomal function in ATMs is hindered, lipid metabolism is affected, and lipid accumulation increases (49). Legumain (Lgmn), a typical lysosomal cysteine protease, is highly expressed in macrophages in response to overfeeding. Lgmn generated from macrophages can inhibit PKA activation and reduce the expression of lipolysis-related proteins through combination with integrin α5β1 in adipocytes, whereas Lgmn-knockout macrophages can regulate lipid metabolism and alleviate insulin resistance (87). However, as evidenced by a previous study, when injected with exogenous recombinant Lgmn, the body weight

and food intake of the mice were significantly reduced (88). Overall, if macrophage function is impaired, dead fat cells cannot be recycled, and lipolysis decreases.

7 Alterations in mitochondrial biogenesis in ATMs

To achieve lipolysis, macrophages require significant energy expenditure to complete the process. However, in obesity, alterations in mitochondrial biogenesis occurring in ATMs lead to macrophage dysfunction. Inflammatory macrophages exhibit increased glycolytic metabolism and decreased mitochondrial oxidative phosphorylation (89). Many factors and mechanisms are involved in the acquisition of mitochondrial metabolic adaptations by macrophages. Fatty acid oxidation (FAO) mainly occurs in the mitochondrial matrix, thus producing ATP. FAO is closely related to M2 polarization. Macrophage programs for mitochondrial biogenesis and fatty acid oxidation are induced in response to IL-4, PPARγ-coactivator-1β (PGC-1β), and signal transducer and activator of transcription 6 (STAT6) (90). During inflammasome-mediated inflammation, histone deacetylase 3 (HDAC3) translocates to mitochondria, leading to deacetylation and a decrease in the activity of HADHA (mitochondrial trifunctional enzyme subunit α) - a key enzyme in mitochondrial fatty acid oxidation, which helps macrophages acquire FAO and mitochondrial morphology adaptations and ultimately promotes IL-1β production (91). In addition, as a member of the PGC-1 family, PGC-1β plays crucial roles in adaptive thermogenesis and mitochondrial fatty acid oxidation (92). As evidenced by a previous study, palmitic acid-induced TNF-α, MCP-1, and IL-1b mRNA and protein expression are reduced by PGC-1β, which can inhibit TAB1/TAK1 complex formation and TAK1 activation, thus decreasing macrophage-induced inflammation (93). Synoviolin (Syvn1), an E3 ubiquitin ligase, is an important target of inflammatory cytokines such as TNF-α, IL-1 and IL-17 (94). Syvn1 can interact with and ubiquitinate PGC-1β, and Syvn1 deficiency results in decreased weight and lipid accumulation. Mechanistically, the expression of PGC-1β target genes is upregulated along with increasement in respiration, basal energy expenditure and the quantity of mitochondria when syvn1 knocked out (95). Additionally, when macrophages are stimulated innately, mitochondrial ROS are produced. These ROS trigger the activation of Fgr kinase, which controls complex II activity and leads to macrophage polarization. The absence of Fgr leads to increased FAO and decreased lipid droplet accumulation after exposure to pathogen-associated molecular patterns (96).

In addition to immune functions such as phagocytosis and cytokine secretion, macrophages are also involved in fat storage and utilization. Many studies have demonstrated that macrophage-deficient mice exhibit weight loss and lean conditions. For example, colony stimulating factor 1 receptor (CSF1R) deletion can eliminate macrophages, resulting in the loss of visceral adipose tissue in rats (97). Additionally, macrophages can regulate energy storage and usage by molecules. Adipose-tissue resident macrophages can secrete PDGF family growth factors to mediate lipid storage. In the absence of PDGFcc, mice exhibit lean conditions through the conversion of extra lipids to thermogenesis or ectopic accumulation (98). Slc6a2 is a norepinephrine (NE) transporter expressing on sympathetic neuron-associated macrophages (SAMs). When Slc6a2 knocked out in SAMs, weight loss in obese mice is significant and consistent, and the proportion of brown adipose tissue is increased due to the decreased clearance of NE, which promotes adaptive thermogenesis and lipid mobilization (99). These results suggest that macrophages play a role in energy storage.

8 Alterations in mitochondrial biogenesis in adipocytes

In addition to changes in mitochondrial biogenesis in macrophages, mitochondrial changes also occur in adipocytes. As the center of metabolism, the mitochondrion is indispensable for survival because it is the main location for aerobic respiration and ATP production. The development and maturation of adipocytes are influenced by mitochondrial function. Early mitochondrial metabolism, biogenesis and ROS production are essential for promoting adipocyte differentiation in an mTORC1-dependent manner (100). Excessive nutrient consumption has been linked to mitochondrial dysfunction (101). Compared with lean people, obese people have mitochondria with reduced oxidation of fatty acids, less defined internal membranes and lower energy generating capacity (102, 103). In addition, adipocytes from high-fat diet-fed mice undergo mitochondrial fragmentation, which reduces their oxidative capacity through a mechanism mediated by the small GTPase RalA, whereas when RalA is deleted, decreased energy expenditure and mitochondrial oxidative phosphorylation are rescued (104). In addition, a study revealed that the interaction substrate of the transcription factor Parkin was accumulating in adipose progenitor cells from obese mice, which suppressed the expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) - a crucial regulator of mitochondrial biogenesis (105).

9 Mitochondria as a bridge connecting ATMs and adipocytes

Previous studies have demonstrated that mitochondria can be transferred between cells to help metabolically challenged cells survive and intercellular mitochondrial transfer is related to several diseases, such as ischemic stroke, allograft rejection and the development of some cancer cells (106–109). Recently, a study

revealed that intercellular mitochondrial transfer also occurs in WAT. Macrophages in WAT can acquire mitochondria from adipocytes *in vivo*, and when Ext1, a gene required for mitochondrial transfer, is genetically deleted, the fat storage increases, whereas energy expenditure decreases (110). A lard-based high-fat diet can inhibit the absorption of mitochondria by macrophages in white adipose tissue while diverting mitochondria released from adipocytes to other organs via the blood (111). In addition, brown adipocytes under thermogenic stress release extracellular vesicles (EVs) containing mitochondrial fragments that have been oxidatively damaged. When reabsorbed by parental brown adipocytes, mitochondria-derived EVs decreased the levels of UCP1 and PPARγ signaling. BAT-resident macrophages eliminate them, which is essential for maintaining BAT function. The aberrant buildup of extracellular mitochondrial vesicles in BAT results from the depletion of macrophages *in vivo*, which inhibits the body's natural thermogenic response to cold exposure (112) (Figure 3).

The secretion of the macrophage cytokine Slit3 from ATMs increased the mRNA levels of UCP1, PGC1α, PRDM16, PPARγ, and Cycs, all of which are associated with thermogenesis. Slit3-overexpressing M2 macrophages can be transferred to WAT, which promotes beiging and thermogenesis (113). Additionally, proinflammatory cytokines secreted from macrophages can affect adipocyte thermogenesis. When cocultured with conditioned media generated from RAW macrophages, the UCP1 mRNA expression level was inhibited in C3H10T1/2 adipocytes. One study demonstrated that TNF-α inhibited transcription factors that bind to the cAMP response element and the UCP1 promoter, thus leading to UCP1 downregulation (114). Additionally, as the master proinflammatory cytokine, the expression of IL-1β is increased in inflammation and obesity. In adipocytes, isoproterenol-induced upregulation of UCP1 can be hindered by IL-1β, which is increased in obese WAT through the activation of extracellular signal-related kinase (ERK). Furthermore, the adipose tissues of mice treated with IL-1β substantially impaired the activation of UCP1 in response to cold (115). In addition to proinflammatory cytokines, anti-inflammatory cytokines are involved in the process of adipocyte thermogenesis. IL-10 usually has an anti-inflammatory effect; however, when IL-10 is ablated, mice exhibit anti-obesity traits, including increased energy expenditure and adipose thermogenesis. Mechanically, IL-10 changes the chromatin architecture and associated transcription factors of thermogenic genes (116). Another cytokine, IL-27 targets adipocytes directly through activating p38 MAPK-PGC-1α signaling and inducing UCP1 synthesis, which makes it a potential therapeutic target for obesity (117). Furthermore, as an anti-inflammatory cytokine, IL-4 can inhibit lipid accumulation and increase the expression of UCP1 in white adipose tissue (118). Altogether, mitochondria can be transferred between macrophages and adipocytes, and cytokines secreted from macrophages can also influence energy consumption in adipocytes.

10 Therapy targets

obesity is an imbalance of energy intake and consumption, actually there is mitochondrial dysfunction in adipocytes, so alleviating mitochondrial damage and increasing thermogenesis are also energy expenditure methods. In addition, obesity is a state of inflammation, and macrophages participate largely in the inflammatory process; thus, decreasing infiltration and hindering the polarization of macrophages is also a major direction of therapy.

10.1 Targeting macrophage recruitment and polarization

Macrophage polarization contributes significantly to the development of obesity. Ubiquitin-specific proteinase 14 (USP14) is highly expressed in ATMs of obese human patients and diet-induced fat mice and can aggravate macrophage recruitment and polarization. However, pharmacological inhibition of USP14 effectively reduces diet-induced hyperlipidemia and insulin resistance in mice, making it an important restraint on the proinflammatory M1 phenotype and therefore limiting obesity-related metabolic disorders (119). Additionally, neuregulin 4 belonging to the epidermal growth factor family is abundant in brown adipose tissue. It reduces inflammation by increasing M1 macrophage death and decreasing

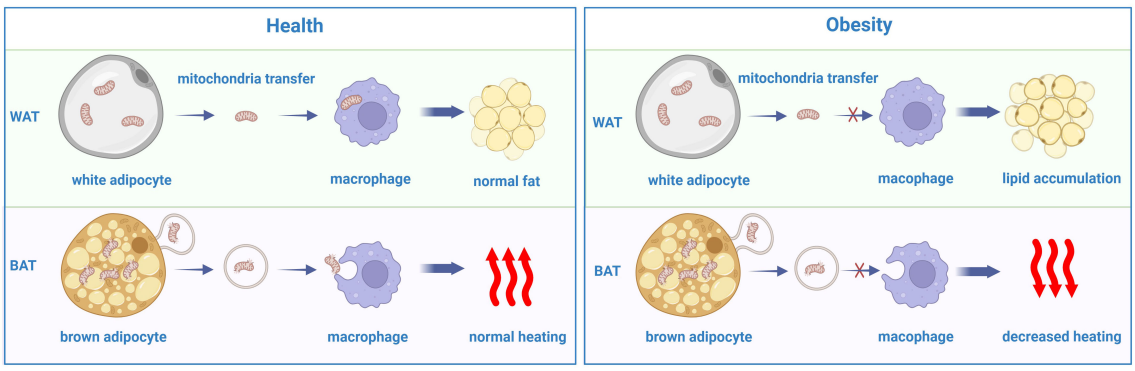

FIGURE 3
The disorder of mitochondrial transfer between adipocytes and macrophages in obesity comparing with the heath.

inflammatory factor release (120). Sirtuin 3 is a mitochondrial deacetylase that comprehensively participates in the regulation of mitochondrial biology. In ATMs from mice feeding a high-fat diet, sirtuin 3 levels were notably decreased. The proinflammatory macrophage polarization caused by palmitic acid was worsened by SIRT3 inhibition or knockdown. Mechanistically, the absence of SIRT3 caused hyperacetylation of succinate dehydrogenase, which in turn caused succinate accumulation. This buildup suppressed the transcription of kruppel-like factor 4 by increasing the level of histone methylation on its promoter, thereby inducing proinflammatory macrophages (121). These findings suggest the protective role of SIRT3. As a member of the adiponectin paralog family, C1q/tumor necrosis factor-related protein 6 (CTRP6) may influence macrophage glycolysis and promote M1 macrophage activation via the PPAR-γ/NF-κB pathway. Both silencing CTRP6 expression and treatment with the PPAR-γ agonist GW1929 can reverse the M1 phenotype effects *in vitro* and *in vivo* through decreasing glycolysis and blocking M1 macrophage polarization (122).

In addition to associated molecules, some drugs also help improve obesity and obesity-related metabolic disorders. Sulforaphane is present in a variety of cruciferous vegetables and has numerous functions. Sulforaphane exhibits a distinct transcriptional pathway that protects against obesity by lowering fatty acid synthesis, promoting ribosome biogenesis and reducing ROS accumulation (123). A recent study demonstrated that sulforaphane plays a role in activating M2 macrophage polarization while inhibiting M1 macrophage polarization, which protects against abnormal extracellular matrix deposition (124). The popular thiazolidinedione pioglitazone has been demonstrated to be effective in preventing cardiovascular problems associated with type 2 diabetes. A study revealed that pioglitazone does not affect cell viability or macrophage differentiation but instead suppress CXCR7 expression, blocking chemotaxis in differentiated macrophages. Furthermore, pioglitazone-induced CXCR7 suppression and chemotaxis inhibition occur through the activation of peroxisome PPARγ in differentiated macrophages (125).

There are also many anti-inflammatory medicines that can reduce cytokine secretion. The primary signaling mechanisms for TNF-α-mediated inflammation involve the NF-κB and MAPK pathways. Cimifugin is a common component of traditional Chinese herbs that can combat inflammatory diseases. It protects against oxidative stress and inflammation by inhibiting the NF-κB/MAPK signaling pathway (126). In 3T3-L1 adipocytes, cimifugin decreases the synthesis of proinflammatory factors and phospho-P65 expression, as well as the activation of the MAPK pathway and accumulation of intracellular lipids (127). In addition, TNF-α-blocking peptides can play a similar role. SN1-13 inhibits TNF-α-mediated signaling by preventing TNF-α and its receptors, and it can regulate the production of inflammatory mediators, including TNF-α, IL-1β, IL-6, and IFN-γ (128). In addition, atorvastatin can reduce CXCR7 mRNA and protein expression and prevent CXCR7 activation to inhibit macrophage migration (129). Although these medicines are not reported for use in the treatment of obesity, inhibiting the expression of proinflammatory cytokines seems to be beneficial for the treatment of obese patients.

10.2 Targeting mitochondria in ATMs

Importantly, mitochondria play a role in thermogenesis, and their structure promotes or inhibits heat production. The mitochondrial calcium uniporter (Mcu) is a multimeric channel in the inner membrane that transports Ca^{2+} to the mitochondrial matrix. Inhibiting Mcu decreases adipocyte differentiation and lipid accumulation, alleviates high-fat diet induced metabolic abnormalities, and increases energy expenditure and thermogenesis (130). Similarly, overexpression of solute carrier family 25 member 28 (SLC25A28), an iron transporter located in the inner mitochondrial membrane, can reduce the development of BAT by downregulating PGC-1α and UCP1, leading to lipolysis inhibition and lipid accumulation (131). Phosphoglycerate mutase member 5 (PGAM5) locating at the mitochondrial outer membrane can be a potential therapeutic target because it can modulate the activation of downstream signaling pathways, such as the NF-κB and MAPK pathways, which in turn controls the expression and synthesis of inflammatory cytokines in macrophages (132).

Activation of PPAR-α and dual PPARα/γ led to the recruitment of $UCP1^{+}$ beige adipocytes and promoted UCP1-independent thermogenesis, resulting in normalized body mass and insulin sensitivity levels (133). A study revealed that miR-155 produced by obese ATMs influences the insulin signaling pathway by targeting PPAR-γ (134). In addition, a recent study revealed that ATM-derived miR-210-3p-enriched EVs increase glucose intolerance, intensify systemic IR, and decrease glucose uptake in adipocytes by directly suppressing GLUT4 expression. However, targeted suppression of miR-210-3p prevents glucose intolerance and insulin resistance in HFD-fed mice (135).

11 Conclusions and perspective

Obesity is a global disease that causes many metabolic diseases. The state of inflammation and decreased energy expenditure are the two most significant features of obesity. Increasing evidence has demonstrated that macrophages participate largely in the development of obesity and inflammation. In obese mice, M2 macrophages are diverted into the M1 macrophage state, which secretes many inflammatory cytokines, causing a systemic and chronic inflammatory state. However, in addition to their inflammatory role, macrophages also perform a phagocytosis function and regulate lipogenesis. Fat accumulation and macrophage changes mutually influence each other. Moreover, mitochondrial dysfunction occurs in both macrophages and adipocytes. Overall, not only macrophage polarization or recruitment but also mitochondria can be potential therapeutic targets for obesity, but further research is needed.

Author contributions

MW: Writing – original draft. MM: Writing – original draft. HD: Writing – review & editing. JM: Writing – original draft,

Writing – review & editing. XL: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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