A review on the biology and properties of adipose tissue macrophages involved in adipose tissue physiological and pathophysiological processes

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Abstract
Obesity exhibits a correlation with metabolic inflammation and endoplasmic reticulum stress, promoting the progression of metabolic disease such as diabetes, hyperlipidemia, hyperuricemia and so on. Adipose tissue macrophages (ATMs) are central players in obesity-associated inflammation and metabolic diseases. Macrophages are involved in lipid and energy metabolism and mitochondrial function in adipocytes. Macrophage polarization is accompanied by metabolic shifting between glycolysis and mitochondrial oxidative phosphorylation. Here, this review focuses on macrophage metabolism linked to functional phenotypes with an emphasis on macrophage polarization in adipose tissue physiological and pathophysiological processes. In particular, the interplay between ATMs and adipocytes in energy metabolism, glycolysis, OXPHOS, iron handing and even interactions with the nervous system have been reviewed. Overall, the understanding of protective and pathogenic roles of ATMs in adipose tissue can potentially provide strategies to prevent and treat obesity-related metabolic disorders.

Keywords: Obesity, Adipose tissue macrophages, White adipose tissue, Brown adipose tissue, Beige adipose tissue, Inflammation, Lipid metabolism, Energy metabolism, Metabolic disorders

Introduction
Adipose tissue can be divided into white adipose tissue (WAT) and brown adipose tissue (BAT); the percentage of WAT is up to 5 to 50% of body weight including subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), and the percentage of BAT decreases with age [1]. Adipose tissue is not only the body’s energy reservoir to insulate against the cold and protect vital organs but also an essential endocrine organ, especially white adipose tissue, which is the main source of endocrine signals [2].

Macrophages are heterogeneous, and their phenotype and functions are regulated by the surrounding micro-environment [3]. Classically activated M1 or proinflammatory macrophages produce proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-12, IL-23, and TNF-α, in response to infection and stress. On the other hand, alternatively activated M2 or anti-inflammatory and immunoregulatory macrophages produce anti-inflammatory cytokines such as IL-10 and TGF-β, contribute to tissue repair, remodeling, and vasculogenesis, and maintain homeostasis [4, 5]. Macrophages exploit protective and pathogenic roles in anti-infection defense, antitumor immunity, metabolic disease development, and even obesity [6].

Adipose tissue macrophages (ATMs) are pivotal players in obesity-associated inflammation and metabolic...
Macrophage polarization in adipose tissues

Classically activated M1 macrophage polarization

The classically activated M1 macrophages are critical players in the initiation and maintenance of adipose tissue inflammation and progression of insulin resistance in the whole body. Fatty acids and LPS as obesogenic factors activate macrophage inositol-requiring enzyme 1a (IRE1α), which represses M2 while enhancing M1 polarization. The development of obesity and metabolic syndrome is enhanced by the macrophage IRE1α pathway by impairing BAT activity and WAT browning [14]. Excess glucose directly affects macrophage activation via the ROCK/JNK and ROCK/ERK pathways, which induce human monocytes and macrophages to undergo M1 polarization upon exposure to high levels of glucose [15]. miR-30 is downregulated in HFD-induced obesity via DNA methylation, thereby inducing Notch1 signaling in ATMs and promoting M1 macrophage polarization [16].

Bone-marrow-derived macrophages isolated from Nfatc3−/− mice treated with IFN-γ and lipopolysaccharide resulted in a reduction in M1 inflammatory markers in vitro, suggesting that Nuclear factors of activated T cells (NFAT) c3 promoted M1 polarization in a cell-autonomous way [17]. Fibronectin type III domain-containing protein 5 (FNDC5), a novel myokine secreted by contracting skeletal muscle, can attenuate inflammation and insulin resistance through AMPK-mediated macrophage polarization in HFD-induced obesity [18].

Alternatively activated M2 macrophage polarization

The alternatively activated M2 macrophages are the predominant macrophage phenotype responsible for anti-inflammation in lean animals. M2 macrophages in adipose tissue inhibited adipocyte progenitor proliferation in the CD206/TGF-β signaling pathway to modulate systemic glucose homeostasis [19]. Deficiency of TLR4 induces the M2-macrophage phenotype and adipose tissue fibrosis [20]. ATMs express NPFFR2, a receptor for the appetite-reducing neuropeptide FF (NPFF), whose plasma levels decrease in obesity, and NPFFR2 deficiency in ATMs abolished both M2 activation and ATM proliferation [21].

It has been indicated that IL-25 stimulates alternatively activated macrophages and their interaction with adipocytes but promotes energy metabolism, enhances mitochondrial functions and attenuates lipid accumulation in the liver and adipose tissues [22]. In addition, cannabinoid receptor 1 (CB1) blockade resulted in downregulation of miR-466 family and miR-762 in ATMs, which promote M2 polarization and macrophage egress from adipose tissue [23]. Empagliflozin, a sodium-glucose cotransporter (SGLT) 2 inhibitor, repressed weight gain by enhancing browning of adipocytes and alleviated obesity-induced inflammation and insulin resistance by polarizing M2 macrophages in WAT and the liver [24]. Similarly, Telmisartan, a well-known antihypertensive drug, was reported to promote the browning of fully differentiated white adipocytes partly through PPAR-mediated M2 polarization [25].

Intriguingly, helminth infection significantly alleviated obesity along with significantly increased Th2/Treg responses and M2 macrophage polarization [26]. Adoptive transfer of helminth-stimulated M2 cells to mice without H. polygyrus infection conferred an obvious improvement of HFD-induced obesity and adipose tissue browning [26]. In some cases, an intracellular glucocorticoid reactivating enzyme 11ß-HSD1 was found to be in the process of switching ATMs from M2 to mixed M1/M2 polarization [27].

Adipocytes impact macrophages polarization

Adipocytes exert effects on ATM phenotypes via a variety of mechanisms. HFD upregulates the ER stress pathway downstream component Chop, a transcription factor C/EBP homologous protein, thereby altering WAT microenvironmental conditions including decreased Th2 cytokine and M1 polarization, resulting in insulin resistance and glucose intolerance [28]. Adipocytes release lipid-laden exosomes (AdExos) that deliver triacylglyceride (TAG) locally to macrophages and are able to induce in vitro differentiation of bone marrow precursors into ATMs [29]. It appears that miR-34a expression is elevated in obesity in part through
suppression of the browning activators fibroblast growth factor 21 (FGF21) and SIRT1 to inhibit fat browning [30]. AdExos carried miR-34a into adipose resident macrophages, resulting in repression of the expression of Krüppel-like factor 4 (Klf4) to control M2 polarization [31]. miR-155-bearing adipocyte-derived microvesicles (ADM) can regulate M1 macrophage polarization [32, 33]. However, exosomes derived from adipose-derived stem cells (ADSCs) transactivate argininase-1 to drive M2 macrophage polarization. M2 macrophages further favor the proliferation of ADSC and the browning of adipose tissue by releasing catecholamine, forming a positive feedback loop [34]. The molecular and epigenetic factors that influence macrophages polarization in both physiologic and pathologic wound healing have been reviewed in [35].

**Adipose tissue macrophage subsets with potential functions**

Scavenging of adipocyte debris is a crucial function of ATMs in obese individuals. Due to their inability to
Potential functions have been reviewed in Table 1. The tissues are protected from hypoxia and ectopic accumulation from remnant lipid droplet through CLS, which is of extracellular lysosomal compartments [36]. ATMs exert lysosomal activity through two vesicles of different pH. One is a neutral lipid vesicle and the other is an acidic-ringed secondary lysosome involved in lipid catabolism, which is formed by fusion of the first vesicle with the primary lysosome [8]. ATMs localize to CLS with various phenotypes. Moreover, MFe ATMs and antioxidant macrophages (Mox) ATMs are essential to iron and oxidative stress handling, respectively. Furthermore, macrophages polarize in both VAT and subcutaneous abdominal adipose tissue. Hence, multiple ATM phenotypes with potential functions have been reviewed in [Table 1].

Macrophones in a crown-like structure of adipose tissues
ATMs adopt a metabolically activated (MMe) phenotype to eliminate dead adipocytes in the way of lysosomal exocytosis [49]. In contrast to classically activated macrophages expressing cell surface markers such as CD38, CD319, and CD274, MMe macrophages specifically overexpress ABCA1, CD36, and PLIN2 regulated by p62 and PPARy [37]. Recently, it has been revealed that MMe macrophages release IL-6 in an NADPH oxidase 2 (NOX2)-dependent manner, which signals through glycoprotein 130 (GP130) on triple-negative breast cancer (TNBC) cells to promote stem-like properties including tumor formation [38]. MMe macrophages exhibit a pleiotrophic effect on tissue environmental homeostasis, which can cause corresponding pathophysiological changes to vary with the progression of obesity. NADPH oxidase 2 (NOX2) has been identified as a driver of the inflammatory and adipocyte-clearing properties of MMe macrophages. Nox2<sup>−/−</sup> mice show mildly improved glucose tolerance in early diet-induced obesity (DIO) compared with wild-type mice due to decreased secretion of inflammatory factors [38]. However, when advanced to late DIO, inactivation of the lysosomal exocytosis function would result in tissue damage due to from severe lipid accumulation [38].

CD9<sup>+</sup> ATMs, which are lipid-laden and localized to CLSs, are responsible for the inflammatory signature of obese adipose tissue, and adoptive transfer of CD9<sup>+</sup> ATMs induces obese-associated inflammation in lean mice [40]. CD9<sup>+</sup> ATMs express higher levels of the surface markers CD16 and CD206 than CD9<sup>−</sup> ATMs and are enriched for transcription factors AP-1 and NF-κB with associated genes such as Ccl2, Il1α, Il1β, and Tnf [40]. In contrast to CD9 ATMs with a signature of metabolic activation, Ly6c ATMs express genes related to angiogenesis and tissue organization. Ly6c ATMs provide normal adipose physiology upon adoptive transfer by inducing genes related to cholesterol and lipid biosynthesis [40].

Recently, a novel and conserved macrophage named lipid-associated macrophage (LAM) with high levels of the lipid receptor Trem2 has been proven to be the predominantly expanded immune cell subset in adipose tissue in multiple obesity-related mouse models [50]. The formation of LAM cells in CLS in adipose tissue is driven by Trem2 signaling, and knockout of Trem2 in bone marrow cells deteriorated the metabolic outcomes of obesity, suggesting that Trem2<sup>+</sup> LAM cells are crucial for the prevention of metabolic disorders upon loss of adipose tissue homeostasis [50].

Iron-rich macrophages in adipose tissues
A study describes a novel population of alternatively activated iron-rich ATMs named MFe<sup>hi</sup>, which display an anti-inflammatory and iron-recycling gene expression profile [42]. MFe<sup>hi</sup> ATMs are capable of storing excess iron from dietary and intraperitoneal supplements mainly through MFe<sup>lo</sup> ATM incorporation to expand the MFe<sup>hi</sup> pool [43]. The impaired iron handling in MFe<sup>hi</sup> ATMs has impacted iron distribution, causing adipocyte iron overload and AT dysfunction in obesity [42]. Compared with LFD-fed mice, HFD-feeding increased Itgax, Ccr7, Tnfα and Il1β expression and decreased M2 marker expression of Stab1 and Clec10a in MFe<sup>hi</sup> ATMs [42].

Antioxidant macrophages in adipose tissues
Oxidized phospholipids (OxPLs) have been identified as endogenous danger associated molecular patterns (DAMPs) with characteristics of oxidative damage to tissues. Macrophages have the capacity to translate tissue oxidation status into either antioxidant or inflammatory responses by sensing OxPLs [46]. Antioxidant macrophages (Mox) respond to OxPLs by upregulating Nrf2-dependent antioxidant enzymes [45] and producing the antioxidant glutathione to suppress regular energy metabolism [46]. A unique population of CX3CR1<sup>neg</sup>/F4/80<sup>low</sup> ATMs that resemble the Mox phenotype (Tnrd1<sup>+</sup>HO1<sup>+</sup>) has been demonstrated to be the predominant ATMs in lean adipose tissue [44].

Macrophones in visceral adipose tissues and subcutaneous adipose tissues
Macrophage polarization in human visceral adipose tissue is related to fatty acid metabolism, cell membrane composition, and diet. CD11c<sup>+</sup>CD163<sup>+</sup> ATMs have been confirmed to accumulate in both VAT and SAT of obese individuals and were found to be clearly correlated with body mass index and production of reactive oxygen
species [27]. Proinflammatory and anti-inflammatory macrophages from human VAT have been determined by flow cytometry as CD14+CD16+CD36high and CD14+CD16−CD163+, respectively [48]. Macrophages in obese adipose tissue are CD11c+CD206+, interpreted to be hybrid M1/M2 macrophages [47].

Other adipose tissue macrophages
Macrophages exhibit correlations with adipocyte accumulation in human skeletal muscles. IL-1β-polarized macrophages (M(IL-1β)) drastically reduced fibroadipogenic progenitors (FAP) adipogenic potential, while IL-4-polarized macrophages (M(IL-4)) enhanced FAP adipogenesis [51]. Tissue-resident NRP1+ macrophages can drive healthy weight gain and maintain glucose tolerance. Ablation of NRP1 in macrophages compromised lipid uptake in these cells, which reduced substrates for fatty acid β-oxidation and shifted energy metabolism of these macrophages toward a more inflammatory glycolytic metabolism [52].

Table 1 Summary of ATMs phenotypes with potential functions in adipose tissues

| Stimulus | transcription factors | Cell surface markers | Cytokines | Functions |
|----------|----------------------|----------------------|-----------|-----------|
| MMe macrophages | High levels of glucose, insulin, and palmitate [37] | p62, PPARγ [37] | ABCA1, CD36, PLIN2 [37] | IL-6 (NOX2-dependent) [38] | Removing dead adipocyte debris [37, 39] |
| CD9 macrophages | AP-1 subunit JunB, NF-kB subunit p65 | CD9, CD16, CD206 | IL-1α, IL-18, TNF | Filled with lipids, and secret exosomes [40] |
| Ly6c macrophages | CTCF [40, 41] | CD11b, Ly6c | Factors that support vascular development and organization |
| MFe hi macrophages | High iron | CD163, Tfrc, Hmox1, ferritin light and heavy chains (Ftl1 and Fth1, respectively), ceruloplasmin(Cp) and ferroportin-1 (Slc40a1) | IL-10 | Iron regulation [42, 43] |
| Antioxidant macrophages (Mox) | | | | Predominant ATMs phenotype in lean adipose tissue. Response to oxidized phospholipids (OxPLs) by upregulating Nrf2-dependent antioxidant enzymes [45]. Antioxidant macrophages (Mox) require suppression of regular energy metabolism to produce the antioxidant glutathione [46]. |
| Hybrid M1/M2 macrophages in human visceral adipose | | | | ATMs phenotype isolated from obese mice [44]. |

Macrophages with different phenotypes perform diverse functions in adipose tissue. MMe macrophages are driven by high levels of glucose, insulin, and palmitate through the p62 and PPARγ pathways, with surface markers such as ABCA1, CD36 and PLIN2. MMe macrophages secrete cytokines such as IL-6 (NOX2-dependent), performing functions that remove dead adipocyte debris. CD9 macrophages are driven through the AP-1 subunit JunB, NF-kB and subunit p65 pathways, possess the surface markers CD9, CD16 and CD206, and secrete cytokines such as IL-1α, IL-18 and TNF. Ly6c macrophages are driven through the CTCF pathway, with their cell surface markers CD11b and Ly6c. Ly6c macrophages perform functions that regulate the adipogenesis process. MFe hi macrophages are driven by high iron, express CD163, Tfrc, Hmox1, ferritin light and heavy chains (Ftl1 and Fth1, respectively), ceruloplasmin (Cp) and ferroportin-1 (Slc40a1). The cell surface markers of antioxidant macrophages (Mox) are CX3CR1neg F4/80loHO1+Txnrd1 [44]. They are predominant ATMs phenotypes in lean adipose tissue and respond to oxidized phospholipids (OxPLs) by upregulating Nrf2-dependent antioxidant enzymes. The cell surface markers of hybrid M1/M2 macrophages are F4/80loCD11c−CD206+. The cell surface markers of macrophages in human visceral adipose are CD11c+CD206−. The cell surface markers of macrophages in human visceral adipose are CD14+CD16+CD163hi and CD14+CD16+CD163−.

Macrophages and adipocytes interact in physiological and pathological events
White adipose tissue serves as an energy-storage organ and plays a homeostatic role in energy dissipation [53]. Moreover, brown adipose tissue generates heat through uncoupled respiration, protecting against hypothermia, hyperglycemia and hyperlipidemia [54, 55]. In addition, beige adipocytes inducibly express mitochondrial uncoupling protein UCP1 in response to cold exposure and
execute a thermogenic and energy-dissipating function interspersed within white adipose tissue [56].

**Macrophage-adipocyte interaction in energy metabolism**

It has been reported that brown adipocytes release CXCL14 to promote adaptive thermogenesis via M2 macrophage recruitment, BAT activation and white fat browning [57]. Likewise, it has been identified that ATM-generated miR-10a-5p is a potential regulator of inflammation in ATMs and induces beige adipogenesis in adipocyte stem cells (ASCs) [58]. Currently, it has been delineated that alkylglycerol-type ether lipids (AKGs) such as breast milk-specific lipid species are metabolized by ATMs to platelet-activating factor (PAF), which ultimately activates IL-6/STAT3 signaling in adipocytes and triggers beige adipose tissue development in infants [59]. In contrast, the partial depletion of CD206+ M2 macrophages elevates the number of beige progenitors in response to cold in genetically engineered CD206DTR mice [60]. M1 macrophages may be partially associated with failure in perigonadal WAT that undergoes browning, as evidenced by removal of macrophages enhancing cold-induced UCP1 expression [61].

Additionally, inflammatory macrophages adhere to adipocytes, mediated by α4 integrin binding to VCAM-1, inhibiting thermogenic UCP1 expression in an Erk-dependent way, thereby impairing beige adipogenesis in obesity [62]. Furthermore, macrophages modulate energy metabolism of WAT in an activation-dependent paracrine way, as evidenced by how CD163\(^{\text{high}}\)/CD40\(^{\text{low}}\) macrophages activated by IL-10/TGF-β downregulated the expression of mitochondrial complex III (UQRC2) gene/protein and ATP-linked respiration, whereas CD40\(^{\text{high}}\)/CD163\(^{\text{low}}\) macrophages activated by LPS/IFN-γ potentiated adipocyte mitochondrial activity [63].

In addition, JAK2, a key mediator downstream of various cytokines and growth factors, which is deficient in macrophages, improves systemic insulin sensitivity and reduces inflammation in VAT and liver in response to metabolic stress [64]. The nuclear lamina is a protein network structure surrounding the nuclear material that participates in a number of intranuclear reactions. Lamin A/C mediates ATM inflammation by activating NF-κB to promote proinflammatory gene expression, hence hastening obesity-associated insulin resistance [65].

**Macrophage-adipocyte interaction in glycolysis and OXPHOS**

Growing evidence has shown that ATMs adopt a unique metabolic profile such as glycolysis and oxidative phosphorylation (OXPHOS), while fatty acid oxidation, glycolysis and glutaminolysis have been reported to facilitate ATMs to release cytokine in lean adipose tissue [66]. Inflammatory macrophages (M1) have metabolic features such as increased succinate-driven Hif1α-dependent glycolysis [66] and reduced phosphorylation, as well as a TCA cycle break-point at ldh [67]. On the other hand, anti-inflammatory macrophages (M2) possess characteristics such as enhanced OXPHOS, UDP-GlcNAc biosynthesis and glutamine-related pathway flows [67]. Cpt2\(^{\text{A/-}}\) mice in which mitochondrial long chain fatty acid β-oxidation was deleted were induced to undergo loss of BAT and a reduction in UCP1 expression by administration of β3-adrenergic (CL-316243) or thyroid hormone (GC-1) agonists, suggesting that adipose fatty acid oxidation is required for the development of BAT during both activation and quiescence [68].

Release of succinate by adipose tissue is a response to hypoxia and hyperglycemia. Succinate receptor 1 (SUCNR1) activation mediates macrophage infiltration and inflammation in obesity, as evidenced by how Suncr1\(^{−/−}\) mice displayed decreased macrophage numbers and increased glucose tolerance [69]. Adipose tissue hypoxia impact on preadipocytes and ATMs in obesity has been reviewed in detail in reference [70].

**Macrophages, adipocytes and nervous system**

The interplay between neuroimmunology and immunometabolism is prevalent within adipose tissue, where immune cells and the sympathetic nervous system play a critical role in metabolic homeostasis and obesity [71]. The interaction between neurons and macrophages has influenced adipocyte biology and whole-body metabolism [72]. Although alternatively activated macrophages do not synthesize relevant amounts of catecholamines [73], a recent study has shown that Ir2s\(^{LysM-/-}\) mice are resistant to obesity upon HFD-feeding via regulation of sympathetic nerve function and catecholamine availability in adipose tissue to activate BAT and beiging of WAT [74]. Macrophage deficient in Ir2s express an anti-inflammatory profile and catecholamine scavenging associated genes to support adipose tissue sympathetic innervation [74].

It has been supposed that neuron-associated macrophages (SAMs) pathologically accumulate in sympathetic nervous system (SNS) nerves of obese subjects in an organ-specific manner, acting as a norepinephrine (NE) sink and exerting proinflammatory activity [75]. Deletion of Mecp2 in CX3CR1 \(^+\) macrophages impeded BAT sympathetic innervation, disrupting NE signaling required for expression of uncoupling protein 1 (UCP1) and BAT thermogenesis [76]. The impairment of catecholamine-induced lipolysis in aging was reversed by alteration of the expression of NLRP3, growth differentiation factor-3(GDF3) and monoamine oxidase A (MAOA) in AT macrophages via regulating the bioavailability of noradrenaline [77].
**Macrophage-adipocyte interactions in other aspects**

The adipose tissue microenvironment interrupts late autophagosome maturation in macrophages, supporting enhanced lipid-droplet (LD) biogenesis and AT foam cell (FC) formation, thereby contributing to AT dysfunction in obesity [78]. Growth/differentiation factor 3 (GDF3) is an activin receptor-like kinase 7 (ALK7) ligand produced from CD11c+ macrophages to control lipolysis and direct ALK7-dependent accumulation of fat in vivo. It has been clarified that the GDF3-ALK7 axis between macrophages and adipocytes is tied to insulin regulation of both fat metabolism and mass [79]. Antigen presentation by either ATMs or adipocytes must be preserved in order to improve systemic glucose metabolism in HFD-fed mice [80]. Specific loss of APC function in ATMs yields mice that are more glucose tolerant. APC function loss in either ATMs or adipocytes, but not both, improves systemic glucose metabolism [80].

**Conclusion**

ATMs responsible for immune surveillance in adipose tissue during HFD-induced obesity are reprogrammed to produce inflammatory and metabolic activated subsets. In addition to M1 and M2 subsets, ATMs with a variety of cell phenotypes to perform their roles in clearance of cellular debris, lipid metabolism, iron storage and energy metabolism in both physiological and pathological states. In summary, the current understanding of the characteristics of the biology and properties of macrophages in adipose tissues facilitates the elucidation of AT polarization, metabolism and regulatory mechanisms. Fully exploration of ATMs functions in obesity can provide potential pharmacologic control points to prevent and treat obesity-related metabolic disorders. Furthermore, the microenvironment of adipose tissues in obesity needs further investigation, especially the epigenetic and transcriptional regulation of the physiological changes of adipocytes from the interplay between ATMs and adipocytes.

**Abbreviations**

ATMs: Adipose tissue macrophages; AT: Adipose tissue; ADM: Adipocyte-derived microvesicles; ASCs: Adipocyte stem cells; AKGs: Alkylglycerol-type ether lipids; ALK7: Activin receptor-like kinase 7; AdExos: Adipocytes release lipid-laden exosomes; BAT: Brown adipose tissue; CB1: Cannabinoid receptor 1; CHOP: C/EBP homologous protein; CLS: Crown-like structure; DAT: deep Adipose tissue; DAMPs: Danger associated molecular patterns; DIO: diet-Induced obesity; ER: Endoplasmic reticulum; FNDC5: Fibronectin type III domain-containing protein 5; FGF21: Fibroblast growth factor 21; FAP: Fibro-adiogenic progenitors; FC: Foam cells; GPD1L: Glycoprotein 130; GDF3: Growth/differentiation factor 3; IRA1α: Inositol-requiring enzyme 1α; Klf4: Krüppel-like factor 4; IL-1β: Interleukin-1β; LAM: Lipid-associated macrophage; LDs: Lipid-droplets; MCP-1: Monocyte chemotactic protein 1; Mox ATMs: Antioxidant macrophages; Mme: Metabolically activated phenotype; M1: Classically activated macrophages; M2: Alternatively activated macrophages; NFATc3: NUCLEAR factors of activated T cells c3; NPF: Neuropeptide FF; NOX2: NADPH oxidase 2; NE: Noradrenaline; OxPLs: Oxidized phospholipids; OxPHOS: Oxidative phosphorylation; PAF: Platelet-activating factor; SAT: Subcutaneous adipose tissue; SGLT: Sodium-glucose cotransporter; SUCLNR1: Succinate receptor 1; SAMS: Neuron-associated macrophages; SNS: Sympathetic nervous system; TATG: Triacylglyceride; TNBC: Triple-negative breast cancer; UCP1: Uncoupling protein 1; UPRs: Unfolded protein reactions; VAT: Visceral adipose tissue; WAT: White adipose tissue

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**Authors’ contributions**

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**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11(1):11–8.
2. O’Rourke RW. Adipose tissue and the physiologic underpinnings of metabolic disease. Surg Obes Relat Dis. 2018;14(11):1755–63.
3. Shapouri-Moghaddam A, Mohammadian S, Vaziri H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol. 2018;233(9):6425–40.
4. Mills CD. Anatomy of a discovery: m1 and m2 macrophages. Front Immunol. 2015;6:212.
5. Wang Y, Smith W, Hao D, He B, Kong L. M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds. Int Immunopharmacol. 2019;70:459–66.
6. Gordon S, Martinez-Pomares L. Physiological roles of macrophages. Pflugers Arch. 2017;469(3–4):365–74.
7. Cinkajzlova A, Mraz M, Haluzik M. Lymphocytes and macrophages in adipose tissue in obesity: markers or makers of subclinical inflammation? Protoplasma. 2017;254(3):1219–32.
8. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. Immunology. 2018;155(4):407–17.
9. Hassnain Waqas SF, Noble A, Hoang AC, Ampenn G, Popp M, Strauss S, et al. Adipose tissue macrophages develop from bone marrow-independent progenitors in Xenopus laevis and mouse. J Leukoc Biol. 2017;102(3):845–55.
10. Amano SU, Cohen JL, Vangala P, Tenceroa M, Nicolozo SM, Yawe JC, et al. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. Cell Metab. 2014;19(1):162–71.
11. Cappellano G, Morandi EM, Rainer J, Grubwieser P, Heize K, Wolfram D, et al. Human macrophages preferentially infiltrate the superficial adipose tissue. Int J Mol Sci. 2018;19(5):1404.
Zhang Y, Mei H, Chang X, Chen F, Zhu Y, Han X. Adipocyte-derived
Pan Y, Hui X, Hoo RLC, Ye D, Chan CYC, Feng T, et al. Adipocyte-secreted
Nakajima S, Koh V, Kuah LF, So J, David L, Lim KS, et al. Accumulation
Torres-Castro I, Arroyo-Camarena UD, Martinez-Reyes CP, Gomez-Arauz
Mehrpouya-Bahrami P, Miranda K, Singh NP, Zumbrun EE, Nagarkatti M.
Feng J, Li L, Ou Z, Li Q, Gong B, Zhao Z, et al. IL-25 stimulates M2
Waqas SFH, Hoang AC, Lin YT, Ampem G, Azegrouz H, Balogh L, et al.
Griffin C, Eter L, Lanzetta N, Abrishami S, Varghese M, McKernan K, et al. TLR4,
Nawaz A, Arminuddin A. CD206(+) M2-like macrophages regulate systemic
Hu L, He F, Huang M, Meng P, Zhou Z, Liu F, et al. NFATc3 deficiency
Xiong XQ, Geng Z, Zhou B, Zhang F, Han Y, Zhou YB, et al. FNDCS attenuates adipose tissue inflammation and insulin resistance via AMPK-mediated macrophage polarization in obesity. Metabolism. 2018;83:31–41.
Nakajima AD, CD206(+) M2-like macrophages regulate systemic glucose metabolism by inhibiting proliferation of adipocyte progenitors. Nat Commun. 2017;8(1):286.
Griffin C, Eter L, Lanzetta N, Abrishami S, Varghese M, McKernan K, et al. TRIF, MyD88 and TLR4 are essential for myelopoiesis and CD11c(+) adipose tissue macrophage production in obese mice. J Biol Chem. 2018;293(23):8775–86.
Waqa SFH, Hoang AC, Lin YT, Ampem G, Azegrouz H, Balogh L, et al. Neutrophilic FFR increases activation and self-renewal of adipose tissue macrophages. J Clin Invest. 2017;127(9):3559.
Feng J, Li L, Ou Z, Li Q, Gong B, Zhao Z, et al. IL-25 stimulates M2 macrophage polarization and thereby promotes mitochondrial respiratory capacity and lipolysis in adipose tissues against obesity. Cell Mol Immunol. 2018;15(5):493–505.
Mehpouya-Bahrami P, Miranda K, Singh NP, Zumbren EE, Nagarkatti M, Nagarkatti PS. Role of microRNA in C1B1 antagonist-mediated regulation of adipose tissue macrophage polarization and chemotaxis during diet-induced obesity. J Biol Chem. 2019;294(19):7669–81.
Xu L, Nagata N, Nagashimada M, Zhuge F, Ni Y, Chen G, et al. SGLT2 inhibition by Empagliflozin promotes fat utilization and Browning and Attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. EBioMedicine. 2017;20:137–49.
Jean EJ, Kim DH, Ahn NH, Choi HE, Cheon HG, Telmisarten induces browning of fully differentiated white adipocytes via M2 macrophage polarization. Sci Rep. 2019;9(1):1236.
Su CW, Chen CY, Li Y, Long SR, Massey W, Kumar DV, et al. Helminth infection protects against high fat diet-induced obesity via induction of alternatively activated macrophages. Sci Rep. 2018;8(1):4607.
Nakajima S, Koh V, Kua LF, So J, Davide L, Lim KS, et al. Accumulation of CD11c+CD163+ adipose tissue macrophages through Uregulation of intracellular 11beta-HSD1 in human obesity. J Immunol. 2016;197(9):3735–45.
Suzuki T, Gao J, Ishigaki Y, Kondo K, Sawada S, Izumi T, et al. ER stress protein CHOP mediates insulin resistance by modulating adipose tissue macrophage polarity. Cell Rep. 2017;18(8):2045–57.
Phaheny SE, Ord, Grijalva A, Xu X, Abele E, Nomanai A. A lipase-independent pathway of lipid release and immune modulation by adipocytes. Science. 2019;363(6430):589–93.
Fu T, Seok S, Choi S, Huang Z, Suino-Powell K, Xu HE, et al. MicroRNA-34a inhibits beige and brown fat formation in obesity in part by suppressing adipocyte fibroblast growth factor 21 signaling and SIRT1 function. Mol Cell Biol. 2014;34(22):4130–42.
Pan Y, Hui X, Hoo RLC, Ye D, Chan CYC, Feng T, et al. Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. J Clin Invest. 2019;129(2):834–49.
Zhang Y, Mei H, Chang X, Chen F, Zhu Y, Han X. Adipocyte-derived microvesicles from obese mice induce M1 macrophage phenotype through secreted mir-155. J Mol Cell Biol. 2016;8(5):505–17.
56. Wu J, Botstrom P, Sparks LM, Ye L, Choi JH, Giang AH, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012;150(2):366–76.
57. Cereijo R, Gavilada-Navarro A, Cairo M, Quesada-Lopez T, Villarroya J, Moron-Ros S, et al. CXCL14, a Brown Adipokine that mediates Brown-fat-to-macrophage communication in Thermogenic adaptation. Cell Metab. 2018;28(5):750–63.
58. Cho YK, Son Y, Kim SN, Song HD, Kim M, Park JH, et al. MicroRNA-10a-5p regulates macrophage polarization and promotes therapeutic adipose tissue remodeling. Mol Metab. 2019;29:98–96.
59. Yu H, Dilbaz S, Cossmann J, Hoang AC, Herwig A, et al. Breast milk alkylglycerols sustain beige adipocytes through adipose tissue macrophages. J Clin Invest. 2019;129(6):2485–99.
60. Igarashi Y, Navaz A, Kado T, Bilal M, Kuwano T, Yamamoto S, et al. Partial depletion of CD206-positive M2-like macrophages induces proliferation of beige progenitors and enhances browning after cold stimulation. Sci Rep. 2018;8(1):14567.
61. Machida K, Okamatsu-Ogura Y, Shin W, Matsuoka S, Kimura K. Role of macrophages in depot-dependent browning of white adipose tissue. J Physiol Sci. 2018;68(5):601–8.
62. Chung KJ, Chataggeorgiou A, Economopoulos M, Garcia-Martin R, Alexaki VI, Mtoulis I, et al. A self-sustained loop of inflammation-driven inhibition of beige adipogenesis in obesity. Nat Immunol. 2017;18(6):654–64.
63. Keuper M, Sachs S, Walheim E, Berti L, Paedle B, Tews D, et al. Activated macrophages control human adipocyte mitochondrial bioenergetics via secreted factors. Mol Metab. 2017;6(10):1226–39.
64. Desai HR, Sivasubramaniam Y, Revelo XS, Schroer SA, Rikkala PR, et al. Macrophage JAK2 deficiency protects against high-fat diet-induced inflammation. Sci Rep. 2017;7(1):7653.
65. Kim Y, Bayona PW, Kim M, Chang J, Hong S, Park Y, et al. Macrophage Lamin a/C regulates inflammation and the development of obesity-induced insulin resistance. Front Immunol. 2018;9:696.
66. Routens L, Hooiveld GJ, Dhingra S, Cramer RA, Netea MG, Stienstra R. Adipose tissue conditioned media support macrophage lipid-droplet biogenesis in obesity: a neuroimmunometabolic perspective. Nat Rev Endocrinol. 2020;16(1):30–43.
67. Blaszczak AM, Wright VP, Anandani K, Liu J, Jalilvand A, Bergin S, et al. Loss of antigen presentation in adipose tissue macrophages or in adipocytes, but not both. Improves Glucose Metab J Immunol. 2019;202(8):2451–9.

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