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EDITED BY
Fernanda Degobbi Tenorio Quirino dos Santos Lopes,
University of São Paulo, Brazil

REVIEWED BY
Sanjeev K. Upadhyay,
Maharaja Sayajirao University of Baroda, India
Karishma Bhatia,
Maharaja Sayajirao University of Baroda, India

*CORRESPONDENCE
Xiao Yuan
yuanxiao1218@163.com

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Targeting macrophage metabolism: mechanisms, cellular crosstalk and implications in obesity-associated metabolic diseases

Chensi Yao[1], Wei Zheng[1], Yamei Jin[1], Jiahao Sheng[2], Mengjiao Kang[2], Jijuan Zhong[1], Min Li[3], Liyun Duan[4,5] and Xiao Yuan[1]*

[1]Department of Endocrinology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China, [2]The First Clinical Medical School, Zhejiang Chinese Medical University, Hangzhou, China, [3]Molecular Biology Laboratory, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [4]The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, China, [5]Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China

Obesity and its associated metabolic disorders constitute a prominent public health challenge. Diverse environmental and metabolic cues trigger alterations in macrophage metabolism, thereby influencing their functional phenotypes. Due to their phenotypic plasticity, macrophages play beneficial roles in tissue homeostasis, yet they also contribute to the progression of metabolic diseases. Consequently, beyond systemic chronic low-grade inflammation, greater attention should be directed toward immunometabolic dysfunction in metabolic tissues during obesity and its related diseases. This review summarizes the functional phenotypes and metabolic characteristics of macrophages, with an emphasis on how tissue niches influence macrophage function in the context of various obesity-related metabolic diseases. Enhanced understanding of the interplay between macrophages and metabolic target organs/tissues may provide novel therapeutic strategies for managing obesity and associated metabolic disorders.

KEYWORDS
inflammation, macrophages, metabolism, obesity-associated metabolic diseases, polarization, reprogramming

1 Introduction

Obesity is a chronic metabolic disorder resulting from an imbalance between energy intake and expenditure, characterized by excessive accumulation of adipose tissue, which often leads to a low-grade, persistent, systemic sterile inflammatory state (1). According to World Health Organization data, over 1 billion people worldwide are currently classified as having obesity, with statistics across all regions showing alarming increases in prevalence rates among all age groups (2), making it a growing global health concern. Mounting evidence indicates that obesity serves as a significant risk factor for multiple metabolic disorders, including insulin resistance (IR), type 2 diabetes (T2D), non-alcoholic fatty liver

disease (NAFLD), dyslipidemia, and cardiovascular diseases (CVD) (3). Over the past two decades, mortality rates from metabolic diseases have steadily increased, with obesity accounting for approximately 40% of these deaths and causing 5 million fatalities in 2019 alone (4).

Current research reveals that disruption of immune-metabolic homeostasis is a hallmark of obesity-related metabolic diseases, where chronic low-grade inflammation is driven not only by immune cell functional impairment, but also by profound phenotypic switching and altered subset distribution of immune cells, alongside excessive production of pro-inflammatory cytokines. This intimate interplay between immunity and metabolism is conceptualized as "immunometabolism" —defined as the changes in intracellular metabolic pathways in immune cells during activation (5). This concept encompasses two interrelated dimensions. At the cellular level, dynamic reprogramming of core metabolic pathways—including glycolysis, the tricarboxylic acid cycle, and lipid and amino acid metabolism—directs immune cell differentiation, polarization, and effector functions. At the systemic level, activated immune cells in turn exert reciprocal effects on whole-body metabolic homeostasis. This bidirectional interplay between immune cells and systemic metabolism has emerged as a central paradigm for understanding obesity-associated metabolic disorders.

As the most crucial innate immune cells, macrophages play a pivotal role in maintaining the balance between homeostasis and disease, including the development of tissues and organs, defense against pathogen invasion, inflammatory responses, and tissue repair. Macrophage infiltration constitutes a primary cause of obesity-related metabolic diseases. Recent research has garnered significant attention regarding the role of macrophage fate and function in regulating and sustaining metabolic homeostasis. Describing macrophage activation states through a relatively extreme binary classification framework based on cellular metabolic differences—where macrophages can polarize into classically (M1) or alternatively (M2) activated subsets—proves highly valuable for understanding immune-metabolic functions in obesity. Although macrophage polarization retains a degree of intrinsic plasticity, these phenotypic states cannot undergo unrestricted or fully reversible interconversion. Instead, they are strongly shaped by local microenvironmental, nutritional, and inflammatory signals, further driving the dynamic progression of obesity-related metabolic disorders across diverse tissues and disease stages.

This review summarizes the classification, functions, and core metabolic regulatory features of macrophages, with a focus on how tissue-resident macrophages sense and respond to metabolic cues in obesity-associated diseases. By integrating current advances in macrophage immunometabolism, we aims to provide theoretical insights for developing novel therapeutic strategies.

2 Origins, polarization and phenotypes of macrophages

Macrophages initiate pro-inflammatory responses by recognizing and phagocytosing pathogens, apoptotic cells, and foreign materials, while also mediating anti-inflammatory tissue repair and immunoregulation to sustain tissue homeostasis (6). Monocytes originate from bone marrow hematopoietic stem and progenitor cells via the mononuclear myeloid lineage. Upon release into the circulation, monocytes are recruited to diverse tissues, where they respond to local microenvironmental cues and terminally differentiate into tissue macrophages with distinct polarization profiles (7). Tissue-resident macrophages (such as Kupffer cells, bronchoalveolar macrophages, microglia, and osteoclasts) display significant heterogeneity and maintain homeostasis by performing crucial tissue-specific functions (8). Most tissue-resident macrophages originate from specific yolk sac-derived progenitors in developing embryos and sustain themselves through self-renewal, though they can also be supplemented by differentiation of bone marrow-derived monocytes (9). Monocyte-derived macrophages, however, are primarily recruited to damaged tissues during injury or inflammation (10).

As highly plastic immune cells, macrophages respond to stimuli such as pathogenic microorganisms, cytokines, fatty acids, and their metabolites within distinct local metabolic and immune environments, exhibiting heterogeneous functional and polarization states. Under normal circumstances, naive macrophages (M0) remain non-polarized. Upon exposure to microenvironmental cues, a "metabolic switch" is activated, reprogramming their metabolic profiles and functional phenotypes to adapt to local signals. Based on their activation states and roles in inflammation, macrophages are broadly categorized into classically activated pro-inflammatory M1-like and alternatively activated anti-inflammatory M2-like phenotypes. Stimulation by lipopolysaccharide (LPS) and interferon-gamma (IFN-γ) drives M1 polarization, activating signaling cascades via pattern recognition receptors (PRRs) such as TLRs and NLRs (11). M1 macrophages secrete pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and inducible nitric oxide synthase (iNOS), exhibiting enhanced phagocytic activity and antigen presentation to clear pathogens, combat tumors, and promote inflammation. M2 macrophages, induced by interleukin-4 (IL-4) and interleukin-13 (IL-13) released from TH2 cells, produce substantial anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonists, and transforming growth factor-β (TGF-β). These macrophages express key genes including arginase 1 (Arg1) and Ym-1, primarily engaging in inflammation suppression, tissue repair, immunoregulation, and defense against helminths and parasitic infections (12). Maintaining the M1/M2 balance is essential for immune homeostasis and normal physiology. In obesity, this balance is disrupted, with an increased proportion of M1 macrophages secreting excessive pro-inflammatory factors. These factors target adipocytes, hepatocytes, and myocytes, interfering with insulin signaling and inducing insulin resistance (13). Moreover, they recruit additional immune cells into adipose tissue and other metabolic organs, amplifying local inflammation and establishing a vicious cycle that drives obesity-associated metabolic disorders. Thus, M1 macrophage overactivation is a key driver of chronic metabolic inflammation.

Beyond the M1/M2 dichotomy, macrophages exhibit remarkable functional diversity driven by distinct transcriptional programs

and stimuli. M2-like macrophages can be further subdivided into M2a, M2b, M2c, and M2d subtypes (Figure 1). These subtypes share the common feature of secreting high levels of the anti-inflammatory cytokine IL-10 and low or undetectable levels of IL-12 (14–16). Most M2 subtypes possess anti-inflammatory and pro-angiogenic properties, secreting growth factors (VEGF, PDGF) and matrix metalloproteinases (MMP2, MMP9) that promote tumor progression (17). M2a (wound-healing macrophages) are induced by IL-4 or IL-13. They suppress excessive inflammation, promote T cell activation and angiogenesis, and secrete profibrotic factors (fibronectin, IGF, TGF-β) to drive tissue remodeling (18). M2b (regulatory macrophages) are activated by LPS or immune complexes via TLR4/Fc receptors. They produce both anti-inflammatory (IL-10, CCL1) and pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-12), functioning to attenuate immune responses while facilitating infection and tumor progression (19). M2c (acquired deactivation macrophages) are induced by glucocorticoids or IL-10-dependent M-CSF signaling. They release high levels of IL-10, CCL18, CCL16, and TGF-β, exhibiting immunosuppressive effects. Characterized by high Mer tyrosine kinase (MerTK) expression, they efficiently phagocytose apoptotic cells and promote proliferation and angiogenesis (17, 20). M2d (tumor-associated macrophages) are polarized by IL-6, TLRs, and adenosine receptors (A2R). They highly express IL-10, TGF-β, and VEGF while showing low expression of IL-12, TNF-α, and IL-1β, thereby promoting tumor angiogenesis, metastasis, and immune tolerance (21, 22). The regulatory balance between M1-like and M2-like phenotypes closely govern immune responses and disease progression.

3 Metabolic reprogramming of macrophages

Macrophages serve dual roles as inflammatory mediators and regulators of immune homeostasis. As key sentinels, macrophages rapidly adapt their metabolic pathways to meet functional demands. Phagocytosis, secretion, and migration are energy-demanding, and their metabolic status is dynamically reprogrammed to support phenotypic activation. In obesity, elevated free fatty acids and a chronic inflammatory state drive immunometabolic reprogramming in macrophages. Under inflammatory conditions, enhanced glycolysis promotes M1 polarization, providing energy for inflammatory responses (23). The expression of glucose transporter-1 (GLUT-1) drives the pro-inflammatory phenotype macrophages by increasing glucose uptake, subsequently enhancing glucose metabolism (24). Furthermore, enhanced pentose phosphate pathway generates abundant nicotinamide adenine dinucleotide phosphate (NADPH), providing substrate for reactive oxygen species (ROS) production and thereby exacerbating inflammatory responses (25). In contrast, oxidative phosphorylation and fatty acid β-oxidation support M2 macrophages, maintaining anti-inflammatory and tissue repair functions at low glycolytic levels (23).

In recent years, the heterogeneity and pleiotropic functions of macrophages in health and disease have gained increasing recognition. Macrophages perform distinct roles across different tissues, yet diverse subsets can also participate in the same disease processes. Their recruitment and persistence at pathological sites are

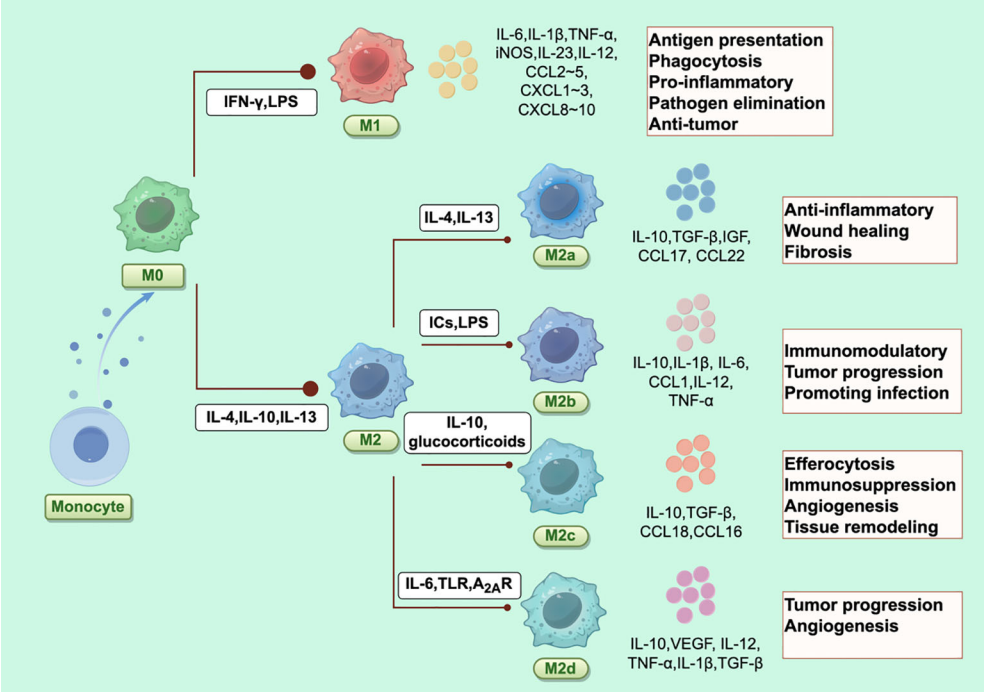

FIGURE 1
Phenotype and function of macrophage polarization.

closely linked to inflammatory diseases. Macrophages reprogram their metabolic pathways in response to microenvironmental signals—including immune responses, inflammation, tissue damage, nutritional changes, and intercellular interactions—to meet dynamic energy and biosynthetic demands. In obesity-related metabolic disorders, these metabolic alterations not only affect intrinsic macrophage function but also drive disease initiation and progression through crosstalk with other metabolically active cells. Therefore, understanding macrophage metabolic regulation is critical for unraveling the pathogenesis of these disorders.

4 Metabolic regulation of different macrophage phenotypes

Macrophage metabolism encompasses nutrient uptake, utilization, and energy production to support cell survival, proliferation, and function. Diverse intra- and extracellular signals remodel metabolic programs that sustain biosynthesis and critically shape immune function (26). Microenvironmental cues drive metabolic reprogramming to orchestrate macrophage activation and polarization, underlying their functional plasticity. Crosstalk among signaling cascades and metabolic pathways (glucose, lipid, and amino acid metabolism) reciprocally influences transcriptional and epigenetic events, leading to distinct functional states (27).In obesity, macrophages encounter a nutrient-saturated microenvironment with elevated fatty acids and glucose, triggering metabolic reprogramming characterized by increased lipid uptake and pathway shifts that profoundly impact macrophage function and inflammation (28). This review summarizes advances in macrophage immunometabolism and key metabolic alterations during phenotypic switching in obesity-associated metabolic diseases.

4.1 Glucose metabolism

In resting immune cells—including macrophages—ATP is primarily generated through oxidative phosphorylation (OXPHOS) to sustain basic cellular functions. Glycolysis converts glucose to pyruvate and can proceed under either aerobic or anaerobic conditions. Under normoxia, pyruvate typically enters mitochondria for conversion to acetyl-CoA and subsequent TCA cycle oxidation. However, upon activation, M1 pro-inflammatory macrophages undergo a metabolic switch toward aerobic glycolysis—the "Warburg effect"—preferentially converting glucose to lactate even when oxygen is abundant (29, 30).

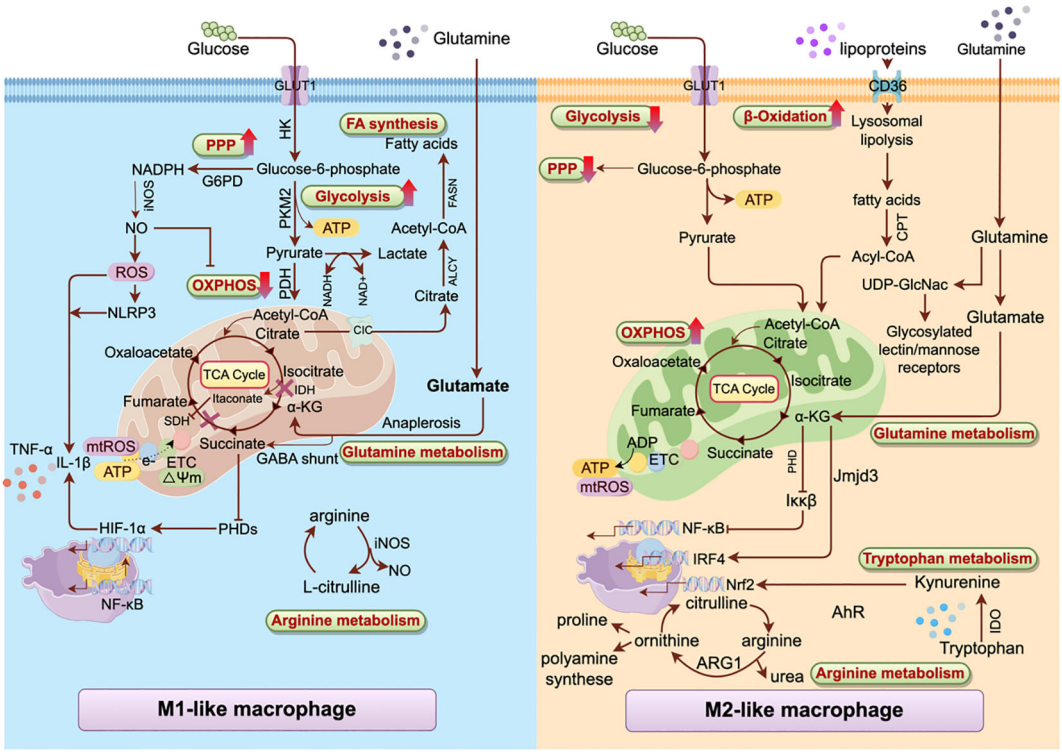

FIGURE 2
Metabolic Regulation Characteristics of Macrophages. In pro-inflammatory (M1-like) macrophages: Aerobic glycolysis is enhanced, converting glucose to lactate, while PPP flux increases to generate NADPH for ROS and NO production. The TCA cycle is disrupted, leading to accumulation of succinate and citrate and reduced OXPHOS. Upregulation of the GABA shunt or glutaminolysis fuels glutamine anaplerosis, further elevating succinate levels. Succinate in turn stabilizes HIF-1α by inhibiting PHDs, thereby inducing pro-inflammatory and glycolytic gene expression. Additionally, arginine is converted to NO and L-citrulline via iNOS. In anti-inflammatory (M2-like) macrophages: Fatty acid oxidation (FAO) is induced, breaking down fatty acids into pyruvate and acetyl-CoA to fuel the TCA cycle and drive OXPHOS as the primary energy pathway. Glycolysis and PPP activity are markedly reduced. Glutamine is catabolized to α-ketoglutarate (α-KG), replenishing TCA intermediates; α-KG exerts anti-inflammatory effects by modulating PHD activity and inhibiting NF-κB signaling. Arginine is converted to ornithine and polyamines by ARG1, with ornithine serving as a precursor for proline synthesis. Arrows: Red = increased flux/activity; Blue = decreased flux/activity.

M1 macrophages display three key metabolic features: enhanced glycolysis, increased pentose phosphate pathway (PPP) flux, and impaired TCA cycle/OXPHOS (Figure 2) (31–33). Aerobic glycolysis produces ATP more rapidly than OXPHOS, albeit with lower efficiency, yielding a net gain of 2 ATP and 2 NADH per glucose molecule. This pathway also generates metabolic intermediates that support nucleotide, amino acid, and fatty acid biosynthesis, as well as NADPH production via the PPP, thereby fueling rapid cellular proliferation and effector functions (34). GLUT1 is a key rate-limiting factor for M1 polarization. GLUT1 overexpression increases glucose uptake and glycolysis, elevates PPP intermediates, reduces oxygen consumption, and drives ROS-mediated pro-inflammatory cytokine production (e.g., IL-1β, IL-6, TNF-α) (24, 35). This ROS burst is essential for the phagocytic activity of M1 macrophages. Consistently, pharmacological inhibition of glycolysis attenuates these pro-inflammatory responses. Of note, while some studies reported that GLUT1 overexpression in certain macrophage cell lines increases glycolytic flux without further inducing IL-6 expression (36), the preponderance of evidence supports a causal role for enhanced glycolysis in driving M1 pro-inflammatory polarization.

Hypoxia-inducible factor-1α (HIF-1α) is a master regulator of this glycolytic switch (37). Under inflammatory conditions, NF-κB activation not only drives pro-inflammatory gene expression but also induces HIF-1α transcription (38, 39). The stability of HIF-1α is further enhanced by TCA cycle intermediates—including succinate, fumarate, and citrate—which inhibit prolyl hydroxylase (PHD) activity (40). Once stabilized, HIF-1α upregulates the expression of GLUT1, glycolytic enzymes, and pyruvate dehydrogenase kinase 1 (PDK1) (41). PDK1 in turn phosphorylates and inhibits pyruvate dehydrogenase (PDH), diverting pyruvate from the TCA cycle toward lactate production, thereby sustaining glycolytic flux (42, 43). Notably, inhibiting the HIF-1α-PDK1 axis has been shown to suppress systemic inflammation and reduce macrophage migration (44).

The role of glycolysis in M2 macrophage activation remains debated. While M2 macrophages are classically associated with OXPHOS, some studies report that IL-4 stimulation can also upregulate glycolysis, mediated by mTORC2-IRF4 or mTORC1 signaling (45, 46). However, this glycolytic increase may be permissive rather than instructive. Using the glycolytic inhibitor 2-deoxy-D-glucose (2-DG), Tan et al. found that PDK1 knockdown suppresses M1 activation but paradoxically enhances IL-4-induced the expression of M2 macrophage markers such as Arg1, YM-1, FIZZ-1, and MRC1 (47). Conversely, Wang et al. demonstrated that 2-DG impairs both glycolysis and OXPHOS, reducing ATP levels and JAK-STAT6 signaling and thereby compromising M2 differentiation. Critically, M2 differentiation proceeds normally when OXPHOS remains intact, even in the absence of glycolytic stimulation (48). Under steady-state conditions, OXPHOS—not glycolysis—is the dominant metabolic pathway across tissue macrophage (49). Thus, targeting OXPHOS may offer a more selective therapeutic strategy for macrophage-related metabolic diseases.

In the context of obesity, sustained exposure to elevated glucose and free fatty acids reinforces the glycolytic bias of adipose tissue macrophages (ATMs), promoting their M1-like polarization and contributing to systemic insulin resistance. These metabolic insights position glycolysis and its regulatory nodes—HIF-1α, PDK1, and GLUT1—as promising therapeutic targets for obesity-associated metabolic disorders.

4.2 Tricarboxylic acid cycle

The TCA cycle is driven by acetyl-CoA reactions, through which NAD^+ and FAD are reduced to NADH and $FADH_2$ in a series of enzymatic reactions. These coenzymes subsequently transfer electrons to the electron transport chain (ETC), enabling OXPHOS and efficient ATP production with oxygen participation. The TCA cycle serves as the central hub regulating macrophage energy metabolism and function. In M1 macrophages, although aerobic glycolysis is the primary energy source, the TCA cycle undergoes multiple interruptions that restrict overall flux. These interruptions lead to the accumulation and mitochondrial escape of specific intermediate metabolites—including citrate, itaconate, and succinate—which subsequently acquire regulatory functions beyond their classical metabolic roles (50).

Two critical breakpoints in the TCA cycle have been identified in pro-inflammatory macrophages. The first breakpoint occurs at isocitrate dehydrogenase (IDH), where inhibited activity causes citrate accumulation and obstructs its conversion to α-ketoglutarate (α-KG), thereby enhancing intracellular lipid synthesis and itaconate production. In the cytosol, citrate is transported via the mitochondrial citrate carrier (CIC) and cleaved by ATP-citrate lyase (ACLY) into acetyl-CoA and oxaloacetate, fueling fatty acid synthesis and providing precursors for pro-inflammatory mediators such as prostaglandins (51, 52). Cytosolic citrate also generates NADPH via ACLY, which is utilized by NADPH oxidase (NOX) and iNOS to produce ROS and NO, respectively, thereby amplifying inflammation (52). In mitochondria, however, citrate-derived itaconate exerts anti-inflammatory effects by activating Nrf2 (which suppresses IL-1β transcription), inducing glutathione and ATF3 (which reduce ROS levels), and negatively regulating pro-inflammatory cytokines (53). The second breakpoint is mediated by itaconate, which accumulates and inhibits succinate dehydrogenase (SDH) activity, leading to elevated succinate levels (54–56). Beyond its intracellular role, succinate released into the extracellular milieu binds to its cognate receptor SUCNR1 (GPR91), further upregulating IL-1β and creating an autocrine amplification loop that sustains inflammation (57, 58). α-KG acts as a counterbalancing metabolite. Derived from glutamine metabolism, α-KG competitively inhibits PHD activity at high concentrations, stabilizing HIF-1α while preventing TCA cycle stagnation. Research indicates that a low α-KG/succinate ratio enhances M1 macrophage activation, while a high α-KG/succinate ratio promotes the M2 phenotype (59). Furthermore, M2 macrophages often rely on glutamine metabolism to supply energy and biosynthetic precursors. Inhibiting glutamine synthetase shifts M2 macrophages toward an M1 phenotype. This shift is characterized by intracellular glutamine depletion and

compensatory enhancement of glycolysis leading to succinate accumulation, which promotes HIF-1α activation (60).

Mitochondrial dysfunction further amplifies this pro-inflammatory program. LPS-stimulated macrophages exhibit elevated mitochondrial membrane potential (ΔΨm), which synergizes with SDH-driven mitochondrial oxidation to promote reverse electron transport (RET)—a process in which electrons flow backward through complex I. RET drives mitochondrial ROS (mtROS) production at complex I, ultimately inducing IL-1β generation (61, 62). mtROS in turn activates MAPK and NF-κB signaling to promote pro-inflammatory gene expression (63) and stabilizes HIF-1α, reinforcing the glycolytic bias and IL-1β production in inflammatory macrophages (64).

Collectively, the TCA cycle in M1 macrophages exhibits a "low-throughput, pro-inflammatory intermediate accumulation" profile. This metabolic framework sustains basal cycling through glutamate/glutamine metabolism while simultaneously amplifying inflammatory signaling via metabolites such as succinate and α-KG. This paradigm prioritizes rapid glycolytic energy supply while repurposing TCA cycle intermediates for immune regulation, represents an adaptive strategy that supports pro-inflammatory macrophage functions. Understanding this metabolic logic opens therapeutic opportunities for chronic inflammatory diseases (e.g., obesity-related metabolic disorders), such as targeting the succinate-HIF-1α axis or modulating glutamate metabolism to curb excessive inflammation.

Unlike M1 metabolism, M2 macrophages exhibit high and intact TCA cycle activity. Following glucose uptake, a portion is utilized for glycogen and fatty acid synthesis to store energy, while pyruvate preferentially enters mitochondria to participate in the TCA cycle. This process generates substantial ATP through OXPHOS, providing ample energy for cellular anabolic metabolism and tissue repair functions. M2 macrophages exhibit high dependence on glutamine metabolism, providing partial substrates for the TCA cycle (50). Following glutaminolysis to glutamate, further conversion to α-KG significantly replenishes TCA cycle intermediate metabolites, sustaining cycle flux to meet high energy demands during anti-inflammatory states.

This metabolic advantage of M2 macrophages is, however, compromised under obese conditions. Beyond promoting TCA cycle intermediate accumulation, obesity induces profound alterations in mitochondrial activity and ETC function in macrophages. Lean adipose tissue macrophages maintain anti-inflammatory phenotypes via OXPHOS through intact ETC complexes. However, in the obese state, adipose tissue macrophages exhibit reduced OXPHOS and impaired ETC function, accompanied by increased glycolytic flux (65, 66). Mechanistically, obesity stabilizes HIF-1α, which upregulates glycolytic enzymes (GLUT1, PGK1, PKM2) and suppresses ETC Complexes I and III (67). This ETC dysfunction promotes electron leakage and mtROS overproduction, which in turn exacerbate pro-inflammatory signaling via NF-κB and MAPK activation (68). Thus, a self-reinforcing loop emerges in which impaired mitochondrial respiration drives glycolytic reprogramming and M1 polarization, while pro-inflammatory signals further exacerbate ETC dysfunction.

4.3 Pentose phosphate pathway

The pentose phosphate pathway (PPP) is upregulated in M1 macrophages and contributes to their pro-inflammatory responses (50). Glucose is initially converted to glucose-6-phosphate (G6P) through the hexokinase reaction, utilizing ATP. G6P can be metabolized via the glycolytic pathway to generate ATP for sustaining cellular function, and can also undergo esterification to produce lipids (triglycerides and phospholipids) (69). Glycolysis also facilitates the channeling of carbon flux into the oxidative PPP. During the oxidative phase, $NADP^+$ is reduced to NADPH, which serves as a coenzyme for iNOS catalytic reactions to facilitate NO production and donates electrons to NADPH oxidase for ROS generation to eliminate pathogens (70, 71).In the non-oxidative phase, glycolytic intermediates are diverted to synthesize ribose-5-phosphate and amino acids. ROS play a crucial role in activating and sustaining M1 macrophages. Studies reveal that PPP restriction significantly reduces intracellular ROS production while sensitizing macrophage polarization toward the M2 (72). In obesity and diabetes, hyperglycemia-induced ROS promotes M1-like polarization (72). Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the PPP and a key regulator of cellular redox balance. G6PD promotes ROS production under stress conditions (73), and its suppression in macrophages attenuates pro-inflammatory responses (74).

Research has revealed G6PD expression is elevated in adipose tissue macrophages of obese animals and positively correlates with pro-inflammatory gene expression. This upregulation promotes oxidative stress and inflammation, potentially through enhanced activation of the p38 MAPK and NF-κB pathways (75). Thus, targeting G6PD activity represents a potential strategy to modulate macrophage function in metabolic diseases. The PPP is also controlled by carbohydrate kinase-like protein (CARKL; sedoheptulose kinase), which catalyzes sedoheptulose-7-phosphate production and modulates carbon flux in the non-oxidative phase, thereby influencing NADPH generation (76). In LPS-activated macrophages, CARKL expression is reduced, leading to increased PPP flux and pro-inflammatory cytokine production. Conversely, IL-4-activated macrophages upregulate CARKL, suppressing PPP activity, reducing NADPH and ROS, and promoting an anti-inflammatory phenotype (76). Therefore, downregulation of CARKL appears crucial for redirecting glucose flux from aerobic metabolism toward glycolysis and the PPP in pro-inflammatory macrophages.

4.4 Lipid metabolism

4.4.1 Fatty-acid synthesis

Beyond alterations in glucose metabolism, fatty acid metabolism also undergoes reprogramming following immune cell activation. The FAS pathway represents a crucial cellular process essential for membrane biosynthesis and energy storage, with fatty acid synthesis being closely associated with the pro-inflammatory effects and signal transduction functions of macrophages (77). In M1

macrophages, fatty acid synthesis (FAS) is markedly enhanced. Mechanistically, citrate accumulation from TCA cycle disruption activates acetyl-CoA carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA—a key precursor for FAS. Malonyl-CoA also inhibits carnitine palmitoyltransferase I (CPT1), thereby blocking fatty acid entry into mitochondria and suppressing fatty acid oxidation (FAO) (78). In obesity, elevated circulating free fatty acids are taken up by macrophages via CD36 and fatty acid transport proteins (FATPs) (79, 80). After internalizing substantial fatty acids, macrophages partially utilize them to synthesize lipids including triglycerides and cholesterol, storing these within lipid droplets. As lipid accumulation progresses, macrophages transform into foam cells, a hallmark of obesity-related metabolic diseases such as atherosclerosis.

During M1 macrophage differentiation of human monocytes stimulated by macrophage colony-stimulating factor (M-CSF), key transcription factors SREBPs (sterol regulatory element-binding proteins) for fatty acid synthesis are upregulated. This process is essential for pseudopodia formation and organelle development in macrophages, demonstrating that FAS is critical for macrophage development and phagocytic activity (81). Researchers have discovered that SREBP-1a not only activates lipogenic genes but also induces Nlrp1a expression, a key component of inflammasome that promotes IL-1β release (82). The pro-inflammatory response in macrophages can be suppressed by inhibiting fatty acid synthase (FASN), a key enzyme of FAS that catalyzes the production of long-chain fatty acids (83). Consistently, myeloid-specific FASN deficiency prevents adipose tissue macrophage recruitment and inflammation in mice (84). Liver X receptor (LXR) signaling regulates macrophage cholesterol metabolism and also influences anti-pathogen responses (85). Activation of LXR promotes M2 macrophage polarization (86), and LXR-α expression suppresses M1 responses and inflammation by inhibiting NF-κB and AP-1 activity while also reducing apoptosis (87).

4.4.2 Beta oxidation

In contrast to the glycolytic metabolism of M1 macrophages, IL-4-induced alternative activation is characterized by enhanced lipid uptake and oxidation (88, 89). Internalized lipids are catabolized in lysosomes to free fatty acids, which are then transported into mitochondria for β-oxidation. FAO supplies acetyl-CoA to the TCA cycle and fuels OXPHOS, providing a sustained energy source for M2 functions (90). Studies have revealed that IL-4 stimulation upregulates STAT6, PPARγ, and PGC-1β, driving FAO and mitochondrial biogenesis. M2 macrophages express higher levels of CPT1, CD36, and medium-chain acyl-CoA dehydrogenase (MCAD) while suppressing pro-inflammatory cytokines (23). PPARγ is essential for the maturation of alternatively activated macrophages. Mice with macrophage-specific PPARγ deficiency exhibit impaired M2 activation, rendering them more susceptible to diet-induced obesity, insulin resistance, and glucose intolerance (91). PPARγ also promotes alternative macrophage activation by promoting glutamate metabolism (92). Glutaminolysis-derived α-KG enhances M2 polarization through Jmjd3-dependent epigenetic regulation and suppresses M1 inflammation by inhibiting the NF-κB pathway (59).

However, considerable debate exists regarding whether FAO is essential for macrophage polarization into the M2 phenotype. Although CPT1 is the rate-limiting enzyme for FAO, several lines of evidence question its necessity. First, high-dose etomoxir (a CPT1 inhibitor) blocks IL-4-induced M2 polarization, but this effect may be due to depletion of intracellular free CoA rather than specific FAO inhibition (93). Second, macrophages from CPT2-deficient mice—which have impaired FAO—retain the capacity to polarize into the M2 phenotype upon IL-4 stimulation (94). Third, FAO inhibition does not affect IL-4-induced gene expression in human macrophages, suggesting species-specific metabolic requirements (95). Collectively, these findings indicate that FAO is dispensable for M2 activation. Instead, FAS may support M2 polarization by providing fuel for OXPHOS (45). Thus, FAO and its metabolites play complex, context-dependent roles in macrophage reparative functions and inflammation.

Beyond mitochondria, peroxisomes also carry out very-long-chain fatty acid (VLCFA) β-oxidation and lipid mediator synthesis, which modulate macrophage inflammatory responses. Peroxisomes form multi-organelle units (mitochondria-ER-peroxisome-lipid droplet clusters) that coordinate inflammatory lipid metabolism. In this context, PPAR signaling in adipose tissue macrophages emerges as an additional node linking peroxisomal function to systemic metabolic improvement in obesity (96, 97). Nevertheless, compared with the well-established mitochondrial ETC-HIF-1α-glycolysis axis, the relative contribution of peroxisomal dysfunction to M1 macrophage polarization remains less defined.

4.5 Amino acid metabolism

4.5.1 Glutamine metabolism

Glutamine metabolism is essential for energy supply and functional maintenance in macrophages, exhibiting distinct metabolic fates in M1 and M2 macrophages. Glutamine can be converted to glutamate via glutaminase, then synergistically produces succinate through either the γ-aminobutyric acid (GABA) shunt pathway or participation in the TCA cycle, thereby providing cellular energy.

In M1 macrophages, glutamine is converted to glutamate via glutaminase, and subsequently to succinate through the γ-aminobutyric acid (GABA) shunt or TCA cycle anaplerosis. This succinate accumulation stabilizes HIF-1α and promotes IL-1β production, as detailed in Section 4.2 (54). Glutamine also contributes to glutathione synthesis and serves as a nitrogen source for nucleotides and amino acids, supporting macrophage activation and inflammatory responses (98).

In M2 macrophages, glutamine metabolism is critical for polarization. Transient glutamine deprivation does not affect M1 markers but markedly suppresses M2 marker expression (Arg1, Mrc1, Ym1, Retnla) and reduces TCA cycle activity (50, 99). Mechanistically, glutamine provides the essential substrate for uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) synthesis—a key metabolite for protein glycosylation and signaling. Tracer

studies have shown that approximately one-third of carbon in TCA cycle metabolites and over half of nitrogen in UDP-GlcNAc originate from glutamine in M2 macrophages (50). Moreover, M2 macrophage glutamine metabolism does not rely entirely on exogenous uptake but can autonomously synthesize glutamine from glutamate and ammonia via glutamine synthetase (GS).

Collectively, these findings establish that glutamine metabolism is indispensable for M2 polarization, whereas M1 macrophages rely less on glutamine. Understanding this differential dependency may inform strategies to selectively modulate macrophage phenotypes in obesity-associated metabolic diseases.

4.5.2 Arginine metabolism

L-arginine, a key amino acid regulating macrophage activation, can be synthesized via citrulline intermediates dependent on glutamine metabolism. Specifically, the metabolic flux catalyzed by iNOS, which converts L-arginine into NO, promotes macrophage polarization toward the M1 phenotype. Conversely, the metabolic pathway catalyzed by Arginase (Arg1) regulates macrophage polarization toward the M2 phenotype (100).

Under pro-inflammatory stimulation with LPS, TNF-α or IFN-γ, M1 macrophages highly express iNOS, an enzyme that catalyzes the conversion of arginine to NO and L-citrulline. NO exerts antibacterial and antiviral effects but also amplifies pro-inflammatory cytokine production (IL-1β, TNF-α). Excessive NO exacerbates tissue damage and inflammation. Notably, iNOS blockade allows LPS/IFN-γ-treated M1 macrophages to repolarize toward an M2 phenotype upon IL-4 stimulation, indicating that NO impedes M1-to-M2 repolarization (33).

M2 macrophages exhibit high expression of Arg1, which catalyzes the hydrolysis of arginine into urea and L-ornithine. The product L-ornithine is further metabolized by ornithine decarboxylase (ODC) into polyamines and proline, which regulate cell proliferation and collagen synthesis, thereby facilitating tissue repair and immune suppression (51). PPAR transcription factors regulate the expression of Arg1 in M2 macrophages. This pathway likely represents the primary mechanism through which tissue-resident macrophages (such as adipose tissue macrophages) acquire the M2-like $Arg1^+$ phenotype. Through M2-like metabolic pathways, these macrophages exert an anti-inflammatory balance in adipose tissue and systemic metabolism (101, 102). Furthermore, Arg1 competes with iNOS for the substrate arginine. Numerous pathogens exploit this mechanism by upregulating arginase expression to restrict arginine availability for iNOS, thereby suppressing NO production (103).

4.5.3 Tryptophan metabolism

Tryptophan metabolism influences macrophage function and polarization through the kynurenine pathway. Tryptophan is catabolized into kynurenine (Kyn) by indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO), and can be further metabolized to downstream products such as quinolinic acid (104, 105). IDO expression is induced by IFN-γ, TNF-α, or prostaglandins. Overexpression of IDO promotes M2 polarization, whereas IDO silencing shifts macrophages toward a pro-inflammatory phenotype (106). Mechanistically, Kyn activates the aryl hydrocarbon receptor (AhR), which inhibits NF-κB signaling, reduces pro-inflammatory cytokine secretion, and favors an anti-inflammatory state (107). In tumor-associated macrophages (TAMs), high IDO expression leads to AhR activation, suppressing Th17 cells and inducing regulatory T cells (Tregs) to promote immune escape (108). Another tryptophan-catabolizing enzyme, interleukin-4-induced gene 1 (IL4I1), is upregulated during BMDM differentiation. IL4I1 degrades L-tryptophan and enhances the M2 phenotype, likely through STAT-6 and STAT-3 phosphorylation (109). Collectively, tryptophan metabolism—primarily via the IDO–Kyn–AhR axis—supports M2 polarization and resolution of inflammation, though the relative contribution of this pathway in obesity-associated metabolic diseases remains to be fully elucidated.

5 Role of macrophages and crosstalk with target cells in obesity-related metabolic diseases

Chronic low–grade inflammation drives obesity, insulin resistance, and T2DM (110). Macrophages serve as key effectors in this process, triggering inflammation and insulin resistance (111). Obesity-induced insulin resistance in metabolic organs arises from both dysfunction of insulin–responsive cells (adipocytes, hepatocytes, and myocytes) and infiltration of pro-inflammatory macrophages. Macrophage accumulation drives tissue inflammation and fibrosis, thereby exacerbating metabolic disorders. Beyond metabolic alterations influencing functional phenotypes, factors such as cellular origin and tissue localization are now considered significant variables determining macrophage biological functions. Accordingly, the regulation of metabolic programs in macrophage populations across distinct microenvironments, as well as their crosstalk with neighboring cells, remains an active area of investigation.

Beyond the classical M1/M2 polarization framework offers instructive value, it cannot fully encompass the true heterogeneity of macrophages in obesity-associated metabolic diseases (112). Single-cell transcriptomics and spatial multi-omics studies based on human samples have revealed that macrophages in adipose tissue and liver are dynamically shaped by local lipid load, glycolytic flux, and hypoxic signals, giving rise to diverse metabolically defined functional subsets (113). They do not simply align with canonical M1 or M2 signatures but instead undergo stage-dependent, tissue-specific functional switching. Lipid-associated macrophages (LAMs), characterized by high expression of TREM2, CD9, and GPNMB, are prominent in both obese adipose tissue and MASLD-affected liver, where they mediate lipid clearance and tissue remodeling (114, 115). Metabolically activated macrophages (MMe) exhibit elevated glycolysis and fatty acid synthesis without the full classical M1 signature; they are enriched in adipose tissue of obese individuals and contribute to insulin resistance (116, 117). Additionally, certain tissue-resident subsets—such as the protective

SerpinB2$^+$ population in visceral adipose tissue—play indispensable roles in preserving insulin sensitivity (118). The presence of these subsets underscores the need to move beyond binary classification and consider macrophage phenotypic diversity in the pathogenesis of obesity-associated metabolic diseases.

In the following sections, we discuss how tissue–specific macrophages in adipose tissue, liver, and pancreatic islets interact with neighboring cells to drive metabolic inflammation and disease progression, while highlighting the metabolic features that underlie their functional plasticity.

5.1 Macrophages and adipose tissue

In obesity, adipose tissue macrophages (ATMs) are central to chronic inflammation and metabolic dysfunction. Adipose tissue comprises white (WAT), brown (BAT), and beige depots, with WAT being the most abundant and primarily responsible for energy storage. ATMs are the most abundant innate immune cells in obese adipose tissue, increasing from 5-10% of total cells in lean states to over 50% in extreme obesity (119). This indicates that obesity significantly alters the macrophage-to-adipocyte ratio. Functionally, ATMs in obesity predominantly adopt an M1 phenotype, secreting pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), whereas lean adipose tissue is dominated by M2 ATMs producing anti-inflammatory IL-10 and TGF-β, thereby promoting inflammation resolution and tissue homeostasis (Figure 3) (120).

With the progression of obesity, ATM polarization shifts from the anti-inflammatory M2 state to the pro-inflammatory M1 phenotype, perpetuating chronic low-grade inflammation characteristic of obesity (121). Nutrient overload triggers adipocyte necrosis and apoptosis. Macrophages cluster around dead adipocytes to clear debris, forming crown-like structures (CLS) (119, 122). Macrophages within CLS store and buffer excess lipids, becoming lipid-laden foam macrophages (123). The number of CLS correlates positively with adipose tissue inflammation and metabolic dysfunction (124). Using single-cell transcriptomics and spatial transcriptomics of murine adipose tissue, Jaitin et al. identified LAMs as a distinct subset characterized by high expression of *Trem2*, *Cd9*, *Lpl*, and *Gpnmb* (114). LAMs are also present in human adipose tissue and differ from both M1 and M2 macrophages. Their transcriptional profile includes both pro-inflammatory genes and lipid metabolism-associated genes, reflecting their specialized function in lipid buffering and tissue remodeling. Trem2$^+$ deficiency in HFD-fed mice led to phenotypic reversal in AT Trem2$^+$ macrophages and reduced lipid accumulation, which was associated with exacerbated adipocyte hypertrophy, systemic lipid accumulation, and glucose intolerance. This highlights that lipid metabolism and accumulation in Trem2$^+$ macrophages may play a protective role in obesity-induced metabolic diseases.

HIF-1α is activated in obese adipose tissue, shifting fuel consumption from OXPHOS to glycolysis and promoting M1 polarization (120, 125). M1–derived inflammatory factors act on

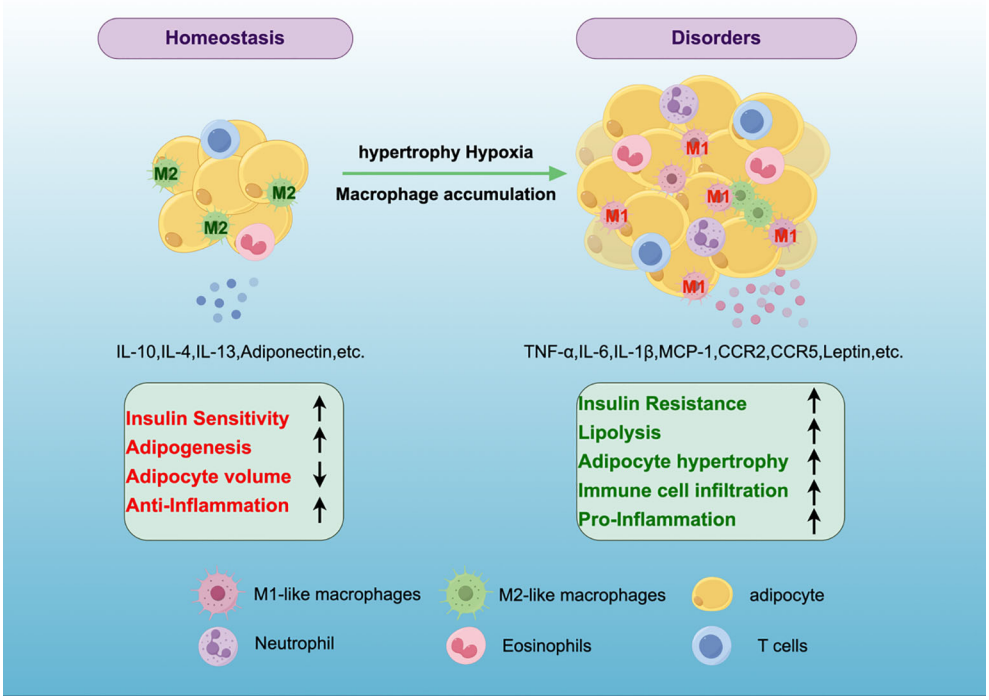

FIGURE 3
Roles of M1-like and M2-like Macrophages in Adipose Tissue. Under lean conditions, adipocytes secrete factors such as adiponectin, which stimulate the predominance of M2-like macrophages in adipose tissue. These M2-like macrophages produce anti-inflammatory cytokines that enhance insulin sensitivity and reduce systemic inflammation. Additionally, they support adipogenesis during adipose tissue remodeling. In obese adipose tissue, excessive lipid accumulation leads to adipocyte hypertrophy and a hypoxic state. Lipolysis releases free fatty acids and various pro-inflammatory adipokines, which promote macrophage polarization toward the M1-like phenotype. These M1-like macrophages produce pro-inflammatory cytokines that interact with receptors on adipocytes, inhibiting insulin signaling pathways and inducing intracellular insulin resistance. This process further exacerbates metabolic disorders.

adipocytes to suppress insulin signaling and induce insulin resistance. In adipose tissue of obese individuals, IL-1β from M1 ATMs activates IKK/NF-κB, leading to serine phosphorylation of IRS-1 and blunting insulin signaling (111). Similar to IKKβ, JNK inhibits insulin signaling via IRS-1 phosphorylation, thereby reducing PI3K/AKT signaling transduction (126, 127). Saturated fatty acids (SFAs) and pro−inflammatory adipokines (e.g., MCP−1, TNF−α) released from hypertrophic adipocytes trigger TLR2/TLR4 signaling in ATMs, activating NF−κB, JNK, and NLRP3 inflammasome assembly, which drives chemokine and cytokine expression and sustains adipose tissue inflammation (128–131). These mechanisms also promote the recruitment and M1 polarization of additional ATMs (132). Inflammation-induced dysfunction of adipocytes accelerates lipid spillover to skeletal muscle and liver, causing ectopic lipid deposition and systemic insulin resistance (110, 133, 134). Additionally, adipocyte-derived microvesicles carrying miR-155 promote M1 ATM polarization, further exacerbating glucose intolerance (135).

Lean adipocytes typically secrete adiponectin, stimulating M2 macrophage polarization (136). Adiponectin is the most abundant adipokine produced by adipocytes; it enhances insulin sensitivity and reduces systemic inflammation, whereas its levels decrease in obese individuals (137). Adiponectin, a well-known AMPK activator, shifts macrophage polarization from M1 to M2 phenotype, thereby suppressing adipose tissue inflammation (138). PPARs are ligand-dependent transcription factors that act as fatty acid sensors in the body, regulating glucose and lipid metabolism (139). Macrophages express multiple free fatty acid receptors, including TLRs, CD36, and G protein-coupled receptors (GPCRs) (140–142). Following receptor binding, SFAs modulate chemokine expression through mechanisms involving ROS generation, NF-κB and PPAR-γ (143). PPAR-δ plays a crucial role in M2 macrophage activation and alleviates diet-induced insulin resistance (144). IL-4 also induces PPAR-δ expression in macrophages, which synergizes with STAT6 to coordinate selectively activated macrophage functions and suppress pro-inflammatory gene expression (145). PPAR-γ has been reported to polarize human monocytes into M2 macrophages *in vitro* (146), whereas myeloid-specific PPAR-γ loss impairs M2 activation and accelerates obesity and insulin resistance in mice (91).

During obesity development, Adipose tissue expansion requires extracellular matrix remodeling and angiogenesis, processes supported by M2-like ATMs. However, rapid adipocyte enlargement outpaces angiogenesis, increasing oxygen consumption and causing local hypoxia, which activates HIF-1α (147). Hypoxia, in turn, induces adipocytes to produce chemokines (MCP-1, LTB4) that recruit immune cells and promote M1 polarization (148). Upregulated CXCL10 and CXCL11 in obese adipose tissue further suppress angiogenesis, exacerbating hypoxia (149). Additionally, macrophages secrete TNF-α, TGF-β, and macrophage-inducible C-type lectin, which suppress adipogenesis and promote adipose tissue fibrosis, ultimately impairing metabolic function (150, 151). Thus, within adipose tissue, macrophages orchestrate lipid and energy metabolism and modulate insulin sensitivity through a network of adipokines and chemokines (152).

5.2 Macrophages and liver tissue

Similar to adipose tissue remodeling in obesity, hepatic macrophages undergo polarization, recruitment, and proliferation during NAFLD pathogenesis (153). Hepatic macrophages—comprising embryo-derived Kupffer cells (KCs) and monocyte-derived infiltrating macrophages—are central to the progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis (154). KCs reside in liver sinusoids and maintain homeostasis by clearing pathogens, phagocytosing cellular debris, regulating iron and lipid metabolism, and preserving immune tolerance (9, 155). Upon metabolic stress, KCs become activated and recruit circulating monocytes, which differentiate into pro-inflammatory macrophages, amplifying liver inflammation (156).

Lipid accumulation in hepatocytes induces lipotoxicity, leading to cell dysfunction and death, which can progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (157). Saturated fatty acids and hepatocyte-derived damage signals (CCL2, TNF-α) activate KCs, promoting their M1-like polarization and the recruitment of $CCR2^{+}Ly6C^{+}$ monocytes, which differentiate into pro-inflammatory macrophages (Figure 4) (158–160). In murine fatty liver models, M1-like macrophages promote triglyceride synthesis via enhanced diacylglycerol acyltransferase activity (161), drive hepatic inflammation through VCAM-1, ICAM-1, and TNF-α (162), and suppress FAO by inhibiting PPAR-α (163). Notably, hepatic macrophage depletion or inhibition of monocyte recruitment prevents steatosis and inflammation in murine NASH models (164). M2-like Kupffer cells ameliorate hepatocyte steatosis and apoptosis in NASH models (165). PPAR-γ/δ can shift KCs toward an M2 phenotype, improving insulin resistance and NAFLD (detailed in Section 4.4) (144, 166). Maternal obesity-induced KCs metabolic reprogramming (HIF-1α-driven glycolysis) predisposes offspring to fatty liver disease (167).

In the steatotic liver, lipid overload drives resident Kupffer cells toward a glycolysis-dominant metabolism, characterized by HIF-1α stabilization and lactate production (168). This metabolic shift is not merely an epiphenomenon but directly instructs pro−inflammatory activation. As detailed in Sections 4.1 and 4.2, this process is driven by itaconate-mediated succinate accumulation and HIF-1α stabilization (56), which is further amplified by a STING-dependent positive feedback loop that sustains M1 polarization (169). Notably, this metabolic-phenotypic coupling is further modulated by specific receptor pathways. In MASLD patients, hepatic $DC\text{-}SIGN^{+}$ macrophages are significantly reduced. These macrophages directly bind to TLR4 and promote its endocytosis, which selectively suppresses MyD88-dependent pro-inflammatory signaling while enhancing TBK1-IRF3 activation, thereby alleviating liver disease (170). Integrative multi-omics analysis identified a $DTNA^{+}$ macrophage subpopulation in the livers of patients with MASH. This subpopulation exhibits M2 polarization features, accompanied by enhanced glycolysis, increased TCA cycle activity, and upregulation of multiple pro-inflammatory pathways. It interacts with activated hepatic stellate cells (HSCs) via the RUNX2-PLG-PARD3 axis, thereby driving MASH progression and liver fibrosis (171).

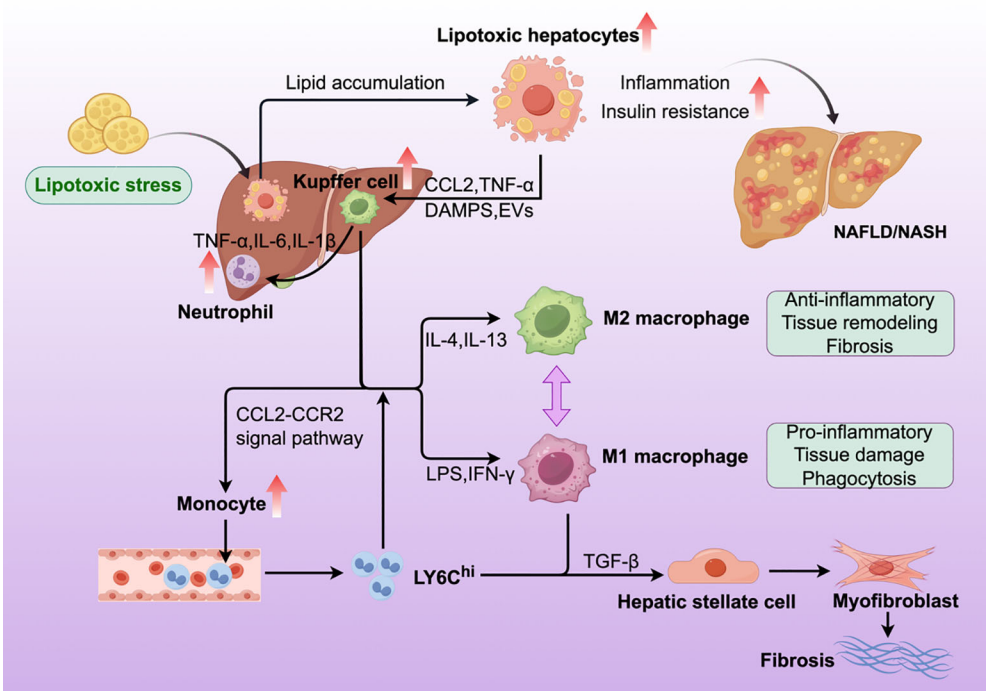

FIGURE 4
Role of Macrophages in Hepatic Tissue in the Context of Obesity. Lipotoxicity-induced hepatocyte injury triggers the release of cytokines and other signals that activate resident macrophages and recruit monocytes and neutrophils. Early infiltrating monocytes differentiate into pro-inflammatory macrophages, aggravating inflammation and insulin resistance. Cytokines from Kupffer cells and monocyte-derived macrophages subsequently activate hepatic stellate cells (HSCs), promoting their transition to myofibroblasts and driving fibrosis. This process ultimately accelerates the progression from NAFLD to NASH.

Spatially resolved multi-omics of 61 human liver samples (10 control, 17 MASLD, 34 MASH) has revealed that LAMs play a protective role in MASLD by clearing lipid droplets and secreting hepatocyte growth factor (HGF) (115). MITF was identified as a key regulator of the lipid-handling capacity of LAMs, and mass spectrometry imaging demonstrated MASLD-specific accumulation of phospholipids potentially linked to LAM-mediated phospholipid metabolism.

HSCs are the primary fibrogenic cells. Hepatocyte loss, inflammation, and metabolic alterations drive their transdifferentiation into myofibroblasts (172). Activated KCs, infiltrating macrophages, and injured hepatocytes secrete profibrogenic factors (e.g., PDGF, TGF-β1) that activate HSCs (173). Macrophages promote NF-κB activation in HSCs via IL-1 and TNF, enhancing myofibroblast survival and accelerating fibrosis (174). Phagocytosis of apoptotic hepatocytes by KCs upregulates death ligands (TNF-α, TRAIL, FasL), inducing further hepatocyte apoptosis and promoting inflammation and fibrosis (173, 175, 176). Residual cholesterol crystals in apoptotic hepatocytes activate the KC NLRP3 inflammasome (177). Foam-like KCs secrete chemokines to recruit monocytes/neutrophils and release TNF-α/TGF-β to activate HSCs, driving hepatic fibrosis (178, 179). Targeting macrophage scavenger receptor MSR1 with monoclonal antibodies prevents lipid-laden macrophage formation and inflammation in preclinical models (180).

Macrophage-derived grancalcin (GCA), which is upregulated in hepatic macrophages of MASH patients and correlates with disease severity, critically mediates macrophage-hepatocyte crosstalk. Mechanistically, GCA triggers TLR9-NF-κB signaling to promote pro-inflammatory cytokines, which induce hepatocyte lipid accumulation and apoptosis, and therapeutic GCA-blocking antibody effectively halts MASH progression (181). Macrophage MRC2 drives MASLD by binding CD147 to activate NF-κB and enhance TNF-α secretion, promoting hepatocyte lipid accumulation (182). As evidenced above, NAFLD progression results from multicellular interactions and dynamic regulation within the hepatic microenvironment. Collectively, understanding how metabolic reprogramming shapes macrophage phenotype—and how macrophage phenotype in turn reshapes tissue metabolism— is not only pathophysiologically critical but also therapeutically actionable.

5.3 Macrophages and pancreatic islet cells

Islet-resident macrophages (IRMs) located adjacent to β-cells act as sensors of β-cell secretory capacity and viability. Their crosstalk with β–cells is central to islet inflammation in diabetes. In obesity–associated T2DM, continuously recruited macrophages drive chronic low–grade inflammation, promoting insulin resistance and β–cell dysfunction (183). Obesity induces localized expansion and accumulation of islet macrophages (184), mediated in part by PDGFR signaling, which contributes to β-cell proliferation defects and secretory dysfunction (185, 186). In T2DM, elevated free fatty acids (FFAs), ROS, and islet amyloid polypeptide (IAPP) promote M1-like macrophage polarization (Figure 5) (187). Islet macrophages sense these metabolic cues and undergo local expansion (188). High glucose and FFAs induce pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, CXCL1) in islets (189, 190). IL-1β, a

key mediator, impairs β-cell function and induces dedifferentiation and apoptosis (187, 191). Palmitate activates the TLR4/NF-κB pathway in macrophages, recruiting M1 cells and impairing β-cell function (192). Phagocytosis of apoptotic β-cells by macrophages triggers efferocytosis-induced ROS and inflammasome activation, further propagating islet dysfunction (193).

IAPP, a peptide hormone synthesized and secreted by pancreatic β-cells, controls postprandial blood sugar levels by delaying gastric emptying and digestion, thereby reducing food intake. IAPP forms amyloid fibrils in T2DM, stimulating macrophage IL-1β secretion and impairing β-cell function (194); depletion of islet macrophages ameliorates this effect (195). Researchers have discovered that activation of free fatty acid receptor FFAR4 (GPR120) in islet macrophages mediates IL-6 release, thereby enhancing glucose-stimulated insulin secretion (GSIS) in lean mice. Yet in both obese type 2 diabetic humans and murine models, this FFAR4-mediated IL-6-dependent insulin secretion is impaired (196). Notably, exogenous IL-6 still improves GSIS in obese/diabetic islets, suggesting therapeutic potential. GPR92 is upregulated in islet macrophages of obese mice; its deficiency worsens glucose homeostasis and M1 polarization, while GPR92 activation promotes anti–inflammatory responses and improves β–cell function (197).

NLRP3 inflammasome activation in islet macrophages contributes to β–cell dysfunction; its deficiency preserves β–cell function in oxidative stress models (198, 199). Islet macrophages sense extracellular ATP (co–secreted with insulin) via purinergic signaling to monitor β–cell activity and maintain islet homeostasis (200, 201). STING activation in macrophages impairs GSIS by promoting phagocytosis of insulin secretory granules (202). M2-like macrophages support β-cell proliferation and survival. In injury models, recruited M2 macrophages promote β-cell regeneration via TGF-β1/SMAD7 and Wnt/β-catenin pathways (203–205).

Beyond phenotypic polarization, IRMs exhibit distinct metabolic features that shape their functional states. Single-cell RNA sequencing of human and mouse islets has revealed that IRMs possess an SLC7A11-driven antioxidant program, which maintains their survival while protecting β-cells from oxidative stress, thereby preserving insulin secretion (206). Conversely, under obese or diabetic conditions, islet macrophages undergo a glycolysis-dominant metabolic switch. In high-fat diet-induced diabetic mice, pancreatic macrophages show increased succinate accumulation and HIF-1α nuclear translocation, leading to enhanced production of pro-inflammatory cytokines and impaired β-cell insulin secretion; these effects can be reversed by the HIF-1α inhibitor PX478 (207). Thus, the succinate/HIF-1α axis represents a key metabolic checkpoint linking macrophage immunometabolism to β-cell dysfunction in T2DM.

Human data support the relevance of these metabolic states. In pancreatic tissues from T2DM patients, $CD68^{+}$ macrophage density

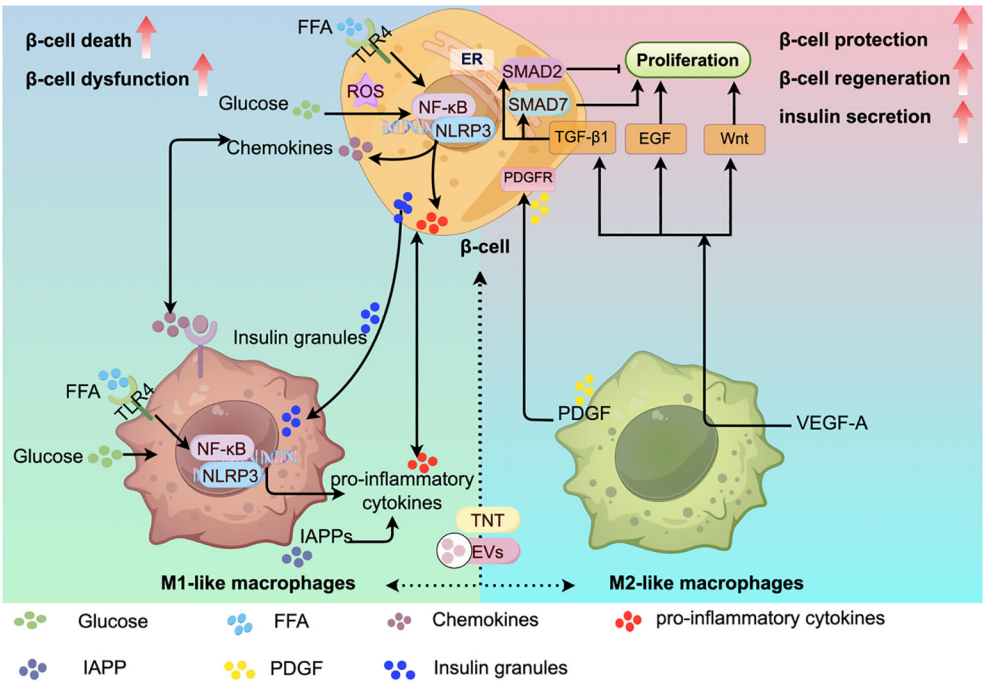

FIGURE 5
Interactions Between Pancreatic β-Cells and M1/M2 Macrophages. Under obese conditions, persistently elevated levels of blood glucose, FFAs, and IAPP promote macrophage polarization toward the M1 phenotype. The local expansion and accumulation of macrophages contribute to chronic islet inflammation, accompanied by the abundant production of various pro-inflammatory cytokines and chemokines. These factors activate inflammatory pathways such as NF-κB and NLRP3, leading to pancreatic β-cell dysfunction and even cell death, ultimately impairing GSIS. In contrast, M2 macrophages secrete various growth factors (e.g., TGF-β1, EGF, PDGF) that support β-cell protection and regeneration. Furthermore, macrophages engage in intercellular communication and material exchange with pancreatic β-cells via extracellular versicles (EVs) and tunneling nanotubes.

correlates positively with the severity of β-cell dysfunction (208). Single-cell transcriptomics of human T2DM islets (n=17) has identified distinct macrophage cytokine signatures (IL15, IFNα1, IFNβ, and IL17F) associated with islet inflammation and β-cell dysfunction (209). These findings underscore that islet macrophages are not a uniform population but rather a heterogeneous ensemble with diverse metabolic and functional states. The translational relevance of these metabolic insights is supported by pharmacological studies. The PPARγ agonist rosiglitazone has been shown to reduce macrophage-mediated β-cell death in type 1 diabetes models by downregulating macrophage heparanase expression, which enhances intra-islet extracellular matrix integrity and reduces immune cell infiltration (210).

Macrophages also communicate with β-cells through extracellular vesicles. Macrophage-derived exosomal miR-155 impairs β-cell function by targeting PDX1 (211), while M1-polarized macrophages transfer miR-212-5p to suppress insulin secretion via the SIRT2/Akt/GSK-3β/β-catenin pathway (212). Additionally, macrophages form tunneling nanotubes (TNTs) for intercellular transport of cytoplasmic material (213), though the relevance of this mechanism in islet biology remains to be explored. In summary, during obesity progression, pancreatic inflammation and β-cell dysfunction are closely associated with islet macrophages. Under homeostasis, macrophages maintain β-cell function, whereas under pathological conditions, they exacerbate β-cell damage through pro-inflammatory polarization, metabolic reprogramming, and intercellular communication.

6 Conclusion and perspectives

Macrophages are widely distributed across multiple tissues and organs throughout the body. By sensing microenvironmental signals and specific stimuli to polarize into pro-inflammatory and anti-inflammatory phenotypes, they coordinate metabolic adaptations and play a critical role in maintaining immune homeostasis. In the emerging field of immunometabolism, metabolic adaptation has been recognized as a key regulator of macrophage-mediated inflammation. Chronic low-grade inflammation contributes directly to obesity-related metabolic diseases—including insulin resistance, T2DM, and NAFLD—by modulating immunometabolic functions across tissues and organs. Therefore, understanding the metabolic characteristics of diverse macrophage populations and their regulatory mechanisms will facilitate the development of therapeutic strategies targeting macrophage metabolism.

Although no approved drugs directly target macrophage metabolism, several glucose-lowering, lipid-lowering, and anti-inflammatory agents in clinical use can indirectly reprogram macrophages, with more specific interventions already in clinical evaluation. Metformin, the first-line therapy for T2DM, inhibits mitochondrial complex I and shifts macrophage metabolism from glycolysis toward oxidative phosphorylation. Its anti-inflammatory effects on macrophages, mediated in part through AMPK activation, have been demonstrated in clinical studies using patient adipose tissue biopsies (214). Transcriptomic analyses of circulating immune cells from treated patients have revealed that SGLT2 inhibitors (dapagliflozin, empagliflozin) suppress M1 activation and promote M2 polarization via the NF-κB, AMPK/mTOR, and JAK/STAT pathways (215). These drugs exert multi-organ protective effects beyond glycemic control and represent promising candidates with immunomodulatory potential. In NASH, the dual CCR2/CCR5 antagonist cenicriviroc promotes M2-dominant polarization; although the Phase III AURORA trial missed its primary fibrosis endpoint, *post-hoc* analyses provided insights for subset-specific designs (216).

Beyond pharmacologic approaches, weight loss strategies such as caloric restriction and bariatric surgery consistently induce an M2-like shift in ATMs. The CALERIE–II trial demonstrated that caloric restriction suppresses adipocyte–derived SPARC, blocking NLRP3 inflammasome priming and JNK–mediated macrophage activation, thereby alleviating obesity–associated metabolic inflammation (217). Advances in nanomedicine enable precise macrophage reprogramming. Biomimetic liposomes and polymer-based nanoparticles have been engineered to achieve targeted delivery to inflammatory macrophages while minimizing off-target effects (218). In parallel, the incorporation of anti-phagocytic moieties such as CD47 on nanocarrier surfaces has been shown to reduce non-specific clearance by phagocytes, thereby improving targeted uptake (219). Beyond drug delivery, gene-therapy nanovesicles that generate cellular itaconate reservoirs have demonstrated the ability to reverse inflammation and restore metabolic function in T2D models by reprogramming macrophage glucose metabolism (220). Collectively, these findings highlight the therapeutic potential of targeting macrophage metabolism, though mechanism–based trials are still needed for clinical translation.

In this review, we have summarized the fundamental metabolic characteristics of macrophages and highlighted how they undergo metabolic rewiring to adapt to changing environmental cues. This underscores the importance of macrophage heterogeneity and plasticity in regulating cellular functions and shaping disease progression. Despite ongoing efforts, our understanding of the intricate regulatory networks within macrophages and between macrophages and their microenvironment remains limited, due to the broad tissue distribution of macrophages and the complexity of regulatory factors.

In obesity-related metabolic diseases, the emerging field of immunometabolism has directed attention toward the metabolic crosstalk between macrophages and target cells/organs (as discussed in Section 5). However, a substantial portion of current knowledge on macrophage metabolism derives from animal studies, and human data remain scarce. Future research should integrate single-cell sequencing, spatial transcriptomics, and high-dimensional multi-omics (proteogenomics, lipidomics, metabolomics) to dissect macrophage subpopulation heterogeneity and dynamic metabolic changes under obese conditions.

In summary, macrophages serve as crucial regulatory nodes in obesity-related metabolic diseases. Elucidating their metabolic reprogramming not only provides a new paradigm for understanding

disease pathogenesis but also lays a vital foundation for developing novel therapeutic strategies.

Author contributions

CY: Conceptualization, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing, Validation. WZ: Software, Visualization, Writing – review & editing. YJ: Software, Visualization, Writing – review & editing. JS: Software, Visualization, Writing – review & editing. MK: Software, Visualization, Writing – review & editing. JZ: Resources, Writing – review & editing. ML: Project administration, Supervision, Writing – review & editing. LD: Funding acquisition, Project administration, Supervision, Writing – review & editing. XY: Conceptualization, Funding acquisition, Project administration, Validation, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work 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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