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REVIEW

Metabolic regulation of tumor-associated macrophage function and immunotherapy in cancer

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ABSTRACT Tumor-associated macrophages (TAMs), essential components of the tumor immune microenvironment (TIME), undergo metabolic reprogramming as part of functional adaptation. Tumor cells modulate TAMs through multiple mechanisms, including metabolic cross-feeding, cytokine production, extracellular vesicles, tumor-derived proteins (such as GRP78) and pathogen-associated patterns (such as Lipopolysaccharide) signaling mediators. In turn, metabolic alterations in TAMs fine-tune TAM function *via* intricate signaling networks with outcomes that vary across cancer types. These functional and phenotypic shifts enable TAMs to influence malignant cells and other TIME components, such as T cells, NK cells, and fibroblasts, through the secretion of inflammatory factors and changes in surface marker expression. This process establishes an extensive network of interconnected cellular crosstalk. In this review the metabolic alterations-intracellular signaling-TAM biology axis is linked to cancer progression contributions and the implications for immunotherapy across diverse malignancies. Building on these insights, current preclinical and clinical studies with a focus on TAMs were surveyed and the advantages and challenges of TAM-targeted therapeutic strategies were systematically evaluated. We anticipate that these perspectives will spur further investigation into TAM-specific immune targets and accelerate the development of next-generation cancer immunotherapies.

KEYWORDS Tumor-associated macrophage; tumor microenvironment; metabolic rewiring; immunotherapy

Introduction

As an abundant immune components in most cancer types, tumor-associated macrophages (TAMs) have a vital role in cancer development as well as therapeutic resistance[1-3]. Global metabolic rewiring takes place in TAMs during the phenotype transition in tumor tissue from pro- to anti-tumor or vice versa[4,5]. A lack of nutrients and oxygen in the tumor microenvironment (TME) results from dysfunctional vasculature, the dramatically increased metabolic demand of malignant cells, and competition from immune and stromal cells[6,7]. This hostile TME favours adaptive cancer cell survival and proliferative mechanisms to promote tumor progression, metastasis, and therapeutic resistance[8,9]. In addition, cancer cells secrete toxic metabolic byproducts, such as adenosine and lactate, to maintain an immunosuppressive TME and evade immune surveillance[10-12]. In particular, TAMs are commonly educated by the TME to support tumor growth. This reprogramming involves a metabolic switch that is intrinsically linked to and enables a phenotypic shift towards a pro-tumor state[13-16]. For example, hypoxic conditions in the TME stabilize hypoxia-inducible factor 1-alpha (HIF-1α) in TAMs, which upregulates glycolytic enzymes and glucose transporters (e.g., Glucose Transporter 1) to promote glycolysis[17,18]. While perivascular TAMs in oxygen-rich niches may use oxidative phosphorylation (OXPHOS) for energy, this process is supported by AMP-activated protein kinase (AMPK) signaling[19]. Metabolic reprogramming in TAMs, which is characterized by enhanced OXPHOS and fatty acid oxidation (FAO), supports the production of anti-inflammatory factors, such as arginase-1 (Arg1), thereby promoting tumor progression and immune evasion[20]. In addition to polarization, metabolic rewiring can regulate macrophage differentiation, mobilization, and phagocytosis[21-23]. Furthermore, diminished phagocytic function is often accompanied by the pro-tumor state to facilitate immune evasion[3,24,25]. Taken together, these findings suggest that targeting metabolic reprogramming in TAMs may enhance the immune response, reduce angiogenesis and metastasis, and synergize with anti-tumoral radiotherapy, chemotherapy, targeted therapy and immunotherapy by remodelling the TME.

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Metabolic reprogramming of TAMs in cancer

Enhanced glycolysis is a vital metabolic shift among classically activated macrophages in response to pathogens or interferon-gamma (IFN-γ)[26]. In contrast, aerobic glycolysis can be upregulated in pro- and anti-inflammatory TAMs to adapt to the hypoxic TME. This adaptation produces rapid energy to support the immunoregulatory, pro-angiogenic, and tissue-remodelling functions within certain TME situations[27-29]. In addition, lactate, a metabolic byproduct of malignant cells, accumulates within the TME. This elevated lactate level upregulates the expression of lactate receptors on TAMs, further promoting glycolysis[30]. In addition, tumoral anti-inflammatory signals, such as colony-stimulating factor-1 (CSF-1), rapidly induce glycolytic metabolism in macrophages to fuel initial pro-tumor activities[31]. As recently reported, CSF-1 synergizes with interleukin-4 (IL-4) to co-opt the protein kinase B-mammalian target of rapamycin pathway, enhancing mitochondrial FAO[32]. This FAO supports the long-term survival, pro-angiogenic, and immunosuppressive functions characteristic of pro-tumor TAMs[33,34]. Both glycolysis and FAO are key mechanisms through which the TME manipulates macrophages to sustain cancer progression. Pro-inflammatory signals, e.g., interleukin 1-beta (IL-1β), IFN-γ, and tumor necrosis factor-alpha (TNF-α), are also present in the TME and maintain a dynamic balance with anti-inflammatory factors[35]. Recently, Jeroundi et al.[36] elucidated new metabolic reprogramming in TAMs in response to GM-CSF plus IFN-γ. These findings suggest that glycogenesis and glycogen accumulation occur in reparative macrophages, whereas a pro-inflammatory stimulus triggers glyconeogenesis in M1-like monocyte-derived TAMs. In the Jeroundi et al. study[36], intracellular lactate, glycerol, and glutamine were proven to be vital substrates for glyconeogenesis, specifically in M1-like TAMs. Furthermore, the Tricarboxylic acid cycle cycle interacts with glycolysis in pro- and anti-tumor TAMs[37].

Another notable metabolic change is the enhanced lipid uptake and storage within TAMs to support pro-tumorigenic functions[38,39]. TAMs internalize the excess lipids and lipoproteins released from the tumor cells. Moreover, TAMs upregulate scavenger receptors, such as CD36 and macrophage scavenger receptor 1 (MSR1), to take up modified lipoproteins and fatty acids from the TME[38,40]. In addition, hypoxia and inflammatory factors, e.g., IL-4 and IL-13, drive lipid droplet formation within TAMs, which serve as energy reservoirs to sustain survival under harsh conditions[41,42]. In addition, TAMs utilize arachidonic acid (AA) to generate prostaglandin E2 (PGE_2), which promotes angiogenesis and immune evasion[13,43-45]. Overall, these metabolic adaptations enable TAMs to support tumor growth and tissue remodelling, which makes lipid metabolism a potential therapeutic target in cancer[46].

Similarly, in mirroring tumor metabolic demands, TAMs exhibit enhanced glutamine uptake and metabolism to support energy production *via* TCA cycle anaplerosis[47,48]. TAMs, especially the anti-inflammatory or pro-tumor macrophages, elevate arginase-1 (Arg1) levels, diverting L-arginine away from nitric oxide (NO) synthesis [*via* inducible nitric oxide synthase (iNOS)] toward polyamine and proline production[49,50]. Furthermore, TAMs have been shown to compete with tumor cells and other immune subsets for cysteine, a critical amino acid for glutathione synthesis[51,52]. Other amino acid metabolic shifts include altered branched-chain amino acid (BCAA) utilization[53], increased trptophan catabolism[54,55], and upregulated serine/glycine biosynthesis or uptake to fuel one-carbon metabolism[56,57].

Notably, TAMs display distinct metabolic profiles and functional roles depending on the location within the TME. This heterogeneity is likely influenced by factors, such as spatial metabolite gradients and variations in macrophage origin. For example, in hypoxic regions, the accumulation of lactate and PGE_2 drives TAM polarization toward a pro-angiogenic phenotype. These TAMs rely predominantly on glycolysis and promote abnormal, leaky angiogenesis through secretion of vascular endothelial growth factor (VEGF) and adrenomedullin (ADM). This pattern is commonly observed in glioblastoma and in the core regions of many solid tumors[58]. Conversely, TAMs often exhibit enhanced OXPHOS activity and active FAO in the tumor-infiltrating margin or stromal areas. These immunomodulatory macrophages highly express immune checkpoints, such as programmed cell death ligand 1 (PD-L1), or deplete arginine *via* Arg1, thereby suppressing T-cell activity[59]. Such characteristics are frequently noted in cancers, including colorectal and breast cancers and pancreatic carcinoma[60].

These metabolic adaptations reinforce immunosuppressive TAM phenotypes to sustain tumor progression. The main metabolic rearrangements during functional transition are summarized in **Figure 1**. While these findings introduce a crucial role of metabolic rewiring of TAMs in tumor progression, the findings raise many questions with respect to mechanisms and therapeutic implications[61,62]. In the section below, we discuss the proposed mechanisms linking metabolic reprogramming to the TAM phenotype and cancer outcome.

Role of metabolism in modulating TAM function

Glucose metabolism

TAMs exhibit a high capacity for glucose uptake[63]. This glucose is not merely used for energy production; glucose metabolites also regulate proteins through post-translational modifications and directly influence TAM phenotype and function by altering metabolic enzyme activity. Furthermore, tumor cells and TAMs engage in a vicious cycle of glucose metabolism that drives tumor progression. In response to stimulation, the

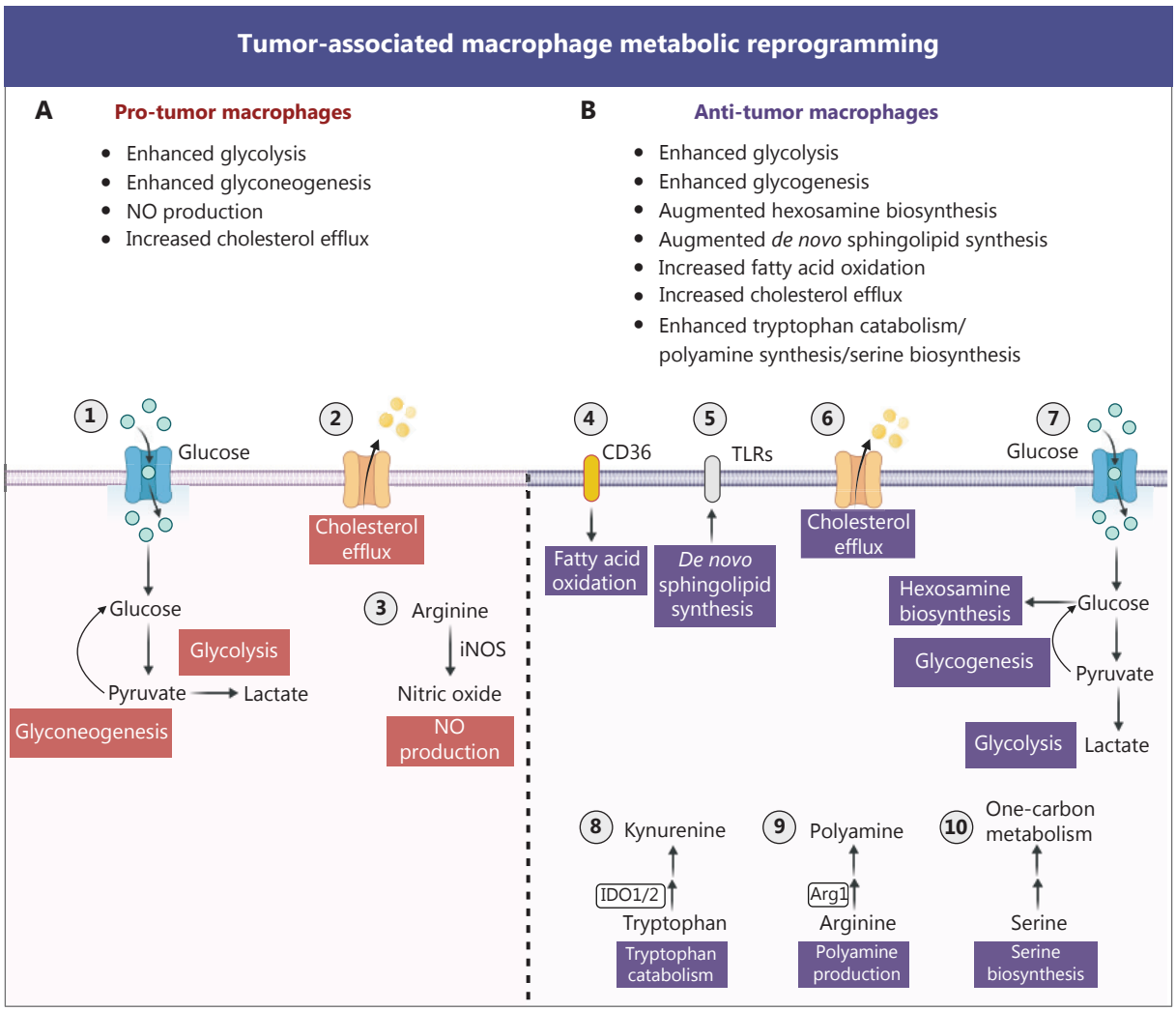


Figure 1 TAM metabolism and rearrangements in the TME. TAMs undergo metabolic rewiring in certain TME situations, in parallel with functional polarization. (A) **Pro-tumor macrophages:** Pro-tumor macrophages exhibit a distinct metabolic profile characterized by the following: ① increased glycolysis and glyconeogenesis fueled by substrates, like lactate; ② enhanced cholesterol efflux; ③ the production of NO from arginine. (B) **Anti-tumor macrophages:** Anti-tumor macrophages require abundant lipids to meet heightened energy and functional demands. Metabolic reprogramming includes the following: ④ enhanced FAO efficacy resulting from increased CD36-mediated lipid uptake; ⑤ increased *de novo* sphingolipid synthesis enables TAM to recognize tumor-derived factors through PRRs, such as TLRs; ⑥ enhanced cholesterol efflux; ⑦ upregulated glycolysis and glycogenesis with increased glucose uptake fueling the hexosamine biosynthesis pathway. Notably, ⑧ tryptophan catabolism is also elevated to produce kynurenine and its derivatives. Furthermore, ⑨ these macrophages elevate arginase-1, diverting L-arginine from NO synthesis toward polyamine production, ⑩ while upregulating serine biosynthesis to fuel one-carbon metabolism. Arg1, Arginase-1; FAO, fatty acid oxidation; IDO1/2, Indoleamine 2,3-dioxygenase 1 and 2; iNOS, Inducible Nitric Oxide Synthase; NO, nitric oxide; PRRs, pattern recognition receptors; TLRs, Toll-like receptors.

activation of pathogen-associated patterns, such as Toll-like receptor (TLR4) or lipopolysaccharide (LPS) stimulation, activate the PI3K/AKT pathway, which leads to upregulation of glycolysis and lactate production, resulting in a pro-inflammatory TAM phenotype[17,64,65]. IL-4 or IL-13 shifts the metabolic program of macrophages toward OXPHOS and FAO in the TME. This transition depends on AMPK activation, which promotes FAO and enhances mitochondrial function. Concurrently, mechanistic target of rapamycin complex 2 (mTORC2) and the Akt–mTORC1 signaling axis are also engaged, although the roles are more selective. For example, IL-4 signaling upregulates ATP-citrate lyase activity through the Akt–mTORC1 pathway, thereby increasing acetyl-CoA levels. This increase in acetyl-CoA facilitates histone acetylation and enhances expression at specific M2 gene loci[66]. By contrast, mTORC1 activation usually upregulates HIF-1α. As a transcription factor,

HIF-α then promotes the expression of glycolytic enzymes, such as lactate dehydrogenasae A (LDHA) and hexokinase 2 (HK2). This enables TAMs to undergo glycolysis, even in the presence of oxygen[67]. Intreastingly, TAMs have been reported to promote glioblastoma cell survival by releasing extracellular vesicles that contain LDHA[68]. Such glycolysis-dependent metabolic reprogramming in macrophages is essential for maintaining metabolic homeostasis. Moreover, glycolytic enzymes and metabolites support the functions of TAMs through intrinsic and moonlighting mechanisms. Hypoxic TAMs accumulate HIF-1α in lung carcinomas, which upregulates HIF-1α target genes encoding glycolytic enzymes (*Slc2a1* and *ldha*)[69]. These glycolytic enzymes, e.g., pyruvate kinase M2 (PKM2) and LDHA, are highly expressed in TAMs, sustaining the TAM functional phenotype transition through distinct mechanisms[70-72]. PKM2 is the rate-limiting enzyme in glycolysis that converts phosphoenolpyruvate (PEP) and adenosine diphosphate to pyruvate and adenosine triphosphate. The direct binding of PKM2 and HIF-1α to hypoxia response element sites in the PD-L1 promoter promotes PD-L1 expression under LPS stimulation in macrophages[73]. Myeloid-specific deletion of LDHA accumulated M1 phenotype macrophages in a K-Ras murine model of lung carcinomas, which was characterized by $CD86^{high}$ and $CCL2^{high}$, and suppressed tumor growth[74].

In addition, the TME soluble factors, such as catabolites, cytokines, and exosomes, have critical roles in modulating TAM glycolysis and coordinating TAM functions. Macrophages located in the peritumoral region exhibit increased glycolysis in hepatocellular carcinoma (HCC) compared to non-tumor liver tissue or circulating monocytes. Mechanistically, the critical regulator of glycolytic flux rate, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), is the major driver of this glycolytic surge, which leads to p65 nuclear translocation and activation of the NF-κB pathway in monocytes. Secreted TNF-α/IL-10 is subsequently elevated and interacts in a loop with receptors on these peritumoral monocytes to increase the expression of the immune checkpoint molecule, PD-L1[75]. Tumor-drived exosomes (TDEs) trigger glycolytic metabolic reprogramming in TAMs and help to maintain the immunosuppressive phenotype. TDEs enhance glucose uptake through NF-κB and the TLR2-dependent pathway, and inhibit mitochondrial OXPHOS to convert pyruvate-to-lactate through nitric oxide synthase 2 (NOS2). The end product, lactate, then feeds back to NF-κB, further increasing PD-L1 expression[17]. In addition to the TME, chronic exposure to environmental factors has been shown to maintain the functional phenotype of TAMs through metabolic reprogramming. It has been shown that smoking tobacco contributes to lung cancer progression through multiple mechanisms, including metabolic reprogramming (e.g., induction of GLUT1) and immune suppression. One potential pathway involves upregulation of factor insulin-like growth factor 2 (IGF2) in the TME, which activates receptors, such as insulin receptors (IRs) on TAMs, leading to increased PD-L1 expression and subsequent inhibition of anti-tumor immunity[76]. Obesity is the common factor of tumor progression. The cytokines and molecules linked to obesity (e.g., leptin, insulin, palmitate, IFN-γ, and TNF) upregulate programmed death-1 (PD-1) expression on TAMs in an mTORC1- and glycolysis-dependent manner. PD-1 acts as a self-inhibitory receptor that suppresses the glycolysis, phagocytosis, and antigen presenting ability of TAMs[77].

The end product of glycolysis, lactate, functions as a signaling molecule and facilitates TAM glucose metabolism to support TAM function through several pathways. Tumor-derived lactic acid, as a soluble factor in the TME, stabilizes HIF-1α and induces *Vegf*/*Arg1* expression in TAMs through integrated metabolic, receptor-mediated, and epigenetic mechanisms. This axis represents a therapeutic vulnerability in cancer[78]. While glucose and glutamine also feed into the TCA cycle, lactate becomes dominant under conditions, such as high extracellular lactate (e.g., the TME). With LPS stimulation under these conditions, lactate-derived acetyl-CoA upregulates acetylation of the histone, H3K27, and this epigenetic modification opens chromatin regions, enabling the transcription of immunosuppressive genes (e.g., *Nuclear Receptor subfamily 4 group A member 1*). This mechanism may be hijacked in tumors to evade immunity[79]. Monocyte-derived macrophages (MDMs) outnumber resident microglia (MGs) in advanced glioblastoma multiforme and become the primary immunosuppressive macrophage population. De Leo et al.[80] reported that tumor-derived factors (e.g., cytokines and metabolites) activate the protein kinase r-like endoplasmic reticulum kinase (PERK)-activating transcription factor 4 (ATF4) axis in myeloid-derived macrophages (MDMs), inducing glucose transporter GLUT1 expression and hyperglycolysis. Lactate modifies histones *via* lactylation [lysine lactylation (Kla)], particularly on the promoters of immunosuppressive genes (e.g., IL-10), thus inhibiting T cell function and furthering tumor growth. Li et al.[81] uncovered how lactate in the TME of colorectal cancer (CRC) epigenetically educates TAMs. Specifically, tumor-derived lactate is taken up by TAMs, which fuels H3K18 lactylation and thuereby suppresses retinoic acid receptor-gamma (RARγ) expression in TAMs, activating NF-κB. This process results in IL-6 production, which activates janus kinase/signal transducer and activator of transcription 3 signalling in CRC cells to promote colorectal tumor growth, progression, and metastasis. This finding identifies a critical metabolic-epigenetic-immune axis driving CRC.

TAMs, specifically pro-tumor M2-like TAMs, exhibit significantly increased glucose uptake to fuel the hexosamine biosynthetic pathway (HBP). The HBP produces UDP-GlcNAc, the donor substrate for a post-translational modification [O-linked β-N-acetylglucosaminylation (O-GlcNAcylation)], which is catalyzed by the enzyme, O-GlcNAc transferase (OGT). O-GlcNAcylation targets cathepsin B (CTSB). Stabilized CTSB is then secreted by TAMs into the surrounding

TME to facilitate tumor cell detachment and migration[82]. Glycolysis co-opts with the TCA cycle in the macrophage phenotype transition.

In addition to enhanced glycolytic flux, studies have revealed a metabolic "break" within the TCA cycle. In pro-inflammatory M1-like states, the TCA cycle is disrupted by isocitrate dehydrogenase (IDH). Under normal conditions, isocitrate is converted to α-ketoglutarate (α-KG) in the TCA cycle, after which α-KG undergoes OXPHOS. This break, also known as "TCA cycle rewiring", involves the diversion of citrate away from oxidative metabolism. Instead, aconitate decarboxylase 1 (Immune-responsive gene 1 (IRG1), encoding aconitate decarboxylase 1) converts cis-aconitate to itaconate, a potent inhibitor of succinate dehydrogenase (SDH), with immunomodulatory properties[26,83]. This conversion causes succinate buildup, stabilizing HIF-1α and inducing IL-1β secretion[84]. As shown, significant disruption in TCA cycle function occurs in TAMs, driven by the unique metabolic demands of the TME. These disruptions fundamentally alter TAM function, promoting immunosuppression and tumor progression.

It has been shown that itaconate is the most highly upregulated metabolite in peritoneal tissue-resident macrophages (pResMΦs) from peritoneal tumors (B16 melanoma or ID8 ovarian carcinoma). Itaconate drives FAO to promote OXPHOS, inducing mitochondrial reactive oxygen species (mtROS) production. mtROS produced by pResMΦs diffuse into neighbouring tumor cells, activating MAPK signalling and ultimately favor tumor cell proliferation and survival[85]. Chen et al.[86] demonstrated that tumor cells activate NF-κB signalling to elevate *Irg1* expression in TAMs. Itaconic acid (ITA) produced by ACOD1 suppresses inflammatory gene expression and $CD8^+$ T cell infiltration within tumor sites by inhibiting ten-eleven translocation DNA dioxygenases. These findings unequivocally identify itaconate as a pro-tumor metabolite. The role of itaconate in driving TAM-mediated immunosuppression makes itaconate a potential therapeutic target for cancer.

In addition to itaconate, cancer cells (particularly lung cancer cells) release high levels of succinate into the TME resulting from reduced succinate dehydrogenase complex iron sulfur subunit B (SDHB) expression or SDH mutation. This process causes succinate buildup, stabilizing HIF-1α and inducing IL-1β secretion[84]. Expression of the succinate receptor 1 (SUCNR1) is also increased in tumor tissue. Extracellular succinate binds to its receptor (SUCNR1) on TAMs to activate the PI3K-HIF1α axis, which stabilizes HIF, thus promoting VEGF secretion and inhibiting T cell function[87]. Zhu et al.[5] reported that the ketogenesis gene, *3-oxoacid CoA-transferase 1*, is highly expressed in TAMs and promotes a pro-tumor phenotype in TAMs by suppressing $CD8^+$ T cell exhaustion. Mechanistically, OXCT1-mediated ketolysis generates succinate as a byproduct in TAMs. Succinate elevates H3K4me3 (histone trimethylation) levels at the promoter of *Arg1*. This change upregulates *Arg1* expression, polarizing TAMs towards a pro-tumor phenotype. Furthermore, Lu et al.[37] revealed that tumor-derived microparticles loaded with succinate (SMPs) remodel polarization of M1-like macrophages by enhancing glycolysis and attenuating the TCA cycle in a protein succinylation–dependent manner. Succinate accumulation from SMPs induces mitochondrial IDH2 succination, which stabilizes HIF-1α. In contrast, succinate induces histone H3K122 succinylation at the LDHA locus in TAMs, which enhances glycolysis and pro-inflammatory polarization, ultimately potentiating anti-tumor immunity.

The concurrent upregulation of glycolysis and reprogramming of the TCA cycle are both essential metabolic adaptations for inflammatory macrophage activation. Upon stimulation with LPS or within the TME, TCA cycle reprogramming leads to the accumulation of specific intermediates, such as itaconate and succinate. These metabolites function as immunomodulatory signalling molecules and participate in inflammatory responses through distinct mechanisms. Concurrently, disruption of the TCA cycle at specific points creates a dependency on upregulated glycolysis. This glycolytic shift provides the necessary ATP for the cellular energetics and biosynthetic precursors required to sustain macrophage effector functions during inflammation. The glucose metabolism-related signaling pathways in TAMs are summarized in **Figure 2**.

Lipid metabolism

Lipid metabolism is central to regulating TAM biology. Lipid metabolism governs the energy supply and the phenotypic state of TAMs through fatty acid metabolism, while specific lipid derivatives function as key signaling molecules. Notably, recent research has revealed that lipid metabolism in TAMs can also act as a "metabolic supplier" for tumor cells[88]. Lipid perturbations impact the immune microenvironment, including TAMs, and have been verified in various cancer types, such as breast cancer, lung cancer, and clear cell renal cell carcinoma (ccRCC). As a prototypical tumor characterized by metabolic reprogramming, the metabolic heterogeneity in the ccRCC TME has recently been well-documented. In the current study macrophages were reported to undergo varying polarization states across distinct metabolic states. For example, $FATTY^+$ macrophages (demonstrating increased fatty acid synthesis metabolic pathway activity) and $amino\ acid^+$ macrophages (exhibiting increased amino acid and glutathione metabolic pathway activity) emerge within pro-inflammatory macrophage subtypes[89].

Lipid metabolism in macrophages is essential for phenotypic reprogramming and considerable progress has been made in elucidating the underlying mechanisms. For example, studies in mouse models have shown that a high-fat diet increases the abundance of lipid-loaded TAMs in the TME, which release CCL6 (the human functional homologue is CCL23) to promote cancer cell migration in prostate adenocarcinoma (PCa). This process is driven by increased expression of the receptor, macrophage receptor with collagenous structure [macrophage receptor with collagenous structure (MACRO) C-type lectin

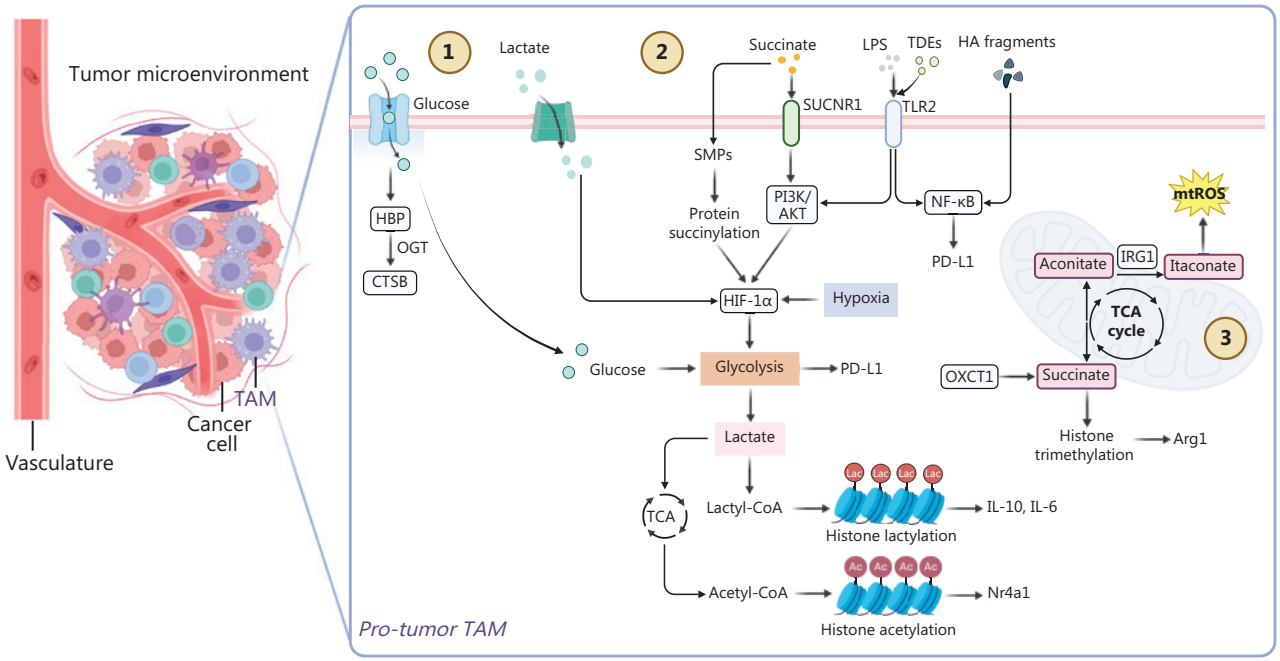


Figure 2 Glucose metabolism in pro-tumor TAMs. Tumor cells and TAMs engage in a vicious cycle of glucose metabolism that drives tumor progression. ① **Increased glucose and lactate levels:** glucose uptake drives HBP, which stabilizes CTSB *via* OGT. Subsequently, TAMs secrete CTSB into the TME, facilitating tumor cell detachment and migration. In contrast, increased glucose uptake and lactate import enhance glycolysis in TAMs and intracellular lactate levels, which promotes immunosuppressive gene expression through epigenetic modifications; ② **Extracellular factors:** tumoral succinate is taken up by TAMs through the receptor, SUCNR1, or *via* SMPs. Once internalized, tumoral succinate stabilizes HIF-1α and drives an immunosuppressive gene expression program through epigenetic modifications. TDEs, tumor-derived HA fragments, and LPS trigger the activation of NF-κB or HIF-1α, thereby upregulating the expression of immunosuppressive genes; ③ **Intermediates:** Reprogramming of the TCA cycle results in the accumulation of specific intermediates, notably itaconate and succinate. Itaconate promotes tumor progression in TAMs by enhancing cancer cell proliferation through the induction of mtROS production. Succinate contributes to pro-tumorigenic gene expression by modulating histone modification. CTSB, cathepsin B; HA, hyaluronan; HBP, hexosamine biosynthetic pathway; IRG1, immune-responsive gene 1; LPS, lipopolysaccharide; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor-kappa B; Nr4a1, nuclear receptor subfamily 4 group A member 1; OGT, O-linked N-acetylglucosamine transferase; OXCT1, oxoacid CoA-transferase 1; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; SMPs, succinate-loaded tumor-derived microparticles; SUCNR1, succinate receptor 1; TDEs, tumor-derived exosomes; TLR2, Toll-like receptor 2. TAMs, Tumor-Associated Macrophages; Arg1, Arginase-1; TCA, Tricarboxylic Acid Cycle; HIF-1α, Hypoxia-Inducible Factor 1α.

domain family 5 member A (CLEC5A)], on macrophages, which is triggered by tumor cell-derived IL-1β. MACRO functions as a scavenger receptor that governs macrophage lipid uptake. In the current study blocking MACRO with an antibody suppressed tumor growth and improved the efficacy of chemotherapy in PCa. This approach may provide a promising anticancer strategy for patients with abnormal lipid metabolism[90]. Peroxisome proliferator-activated receptor-gamma (PPARγ) is a nuclear hormone receptor that senses cellular fatty acid levels and coordinates lipid transport by regulating *fabp5* gene expression. PPARγ has been reported to be involved in the function of fatty acid-binding protein 5 (FABP5$^+$) lipid-loaded TAMs. Specifically, tumor cells secrete long-chain unsaturated fatty acids, including docosahexaenoic acid (DHA), which are taken up by TAMs. FABP5 transports these fatty acids to the nucleus inside TAMs, leading to activation of PPARγ. This activation drives the upregulation of immunosuppressive genes, like *PD-L1*, *PD-L2*, and *Gal-1*. By suppressing effector T cell proliferation and activation, this pathway ultimately facilitates HCC progression[91]. In addition, pyruvate kinase M2 (PKM2) drives the Warburg effect in macrophages and interacts with HIF-1α to upregulate the expression of glycolytic enzymes, such as GLUT1 and LDHA[92]. Tumoral exosomal PKM2 can polarize TAMs to an anti-inflammatory phenotype to enhance the proliferation, migration, and invasion of gastric cancer (GC) cells. Mechanistically, exosomal PKM2 increases the accumulation of sterol regulatory element-binding protein 1 (SREBP1) in the nucleus to upregulate fatty acid synthesis-related enzymes [e.g., fatty acid synthase (FASN), acetyl-CoA carboxylase alpha (ACACA), and ATP citrate lyase (ACLY)][93]. In addition to lipid synthesis, phenotype rewiring in TAMs can also be achieved through lipid catabolism and FAO. Tian et al.[94] identified glucose-regulated protein 78 (GRP78), which is secreted by colon cancer cells, as a regulator of TAM polarization. GRP78 enters

macrophages and localizes to lipid droplets, enhancing the stability of adipose triglyceride lipase (ATGL). This process polarizes macrophages towards an anti-inflammatory phenotype mediated by interactions among AA, DHA, and PPARγ[94]. As the tumor progresses, the predominant subtype of TAMs becomes M2-like, which is accompanied by improved efficacy of FAO. Blocking FAO with perhexiline (PerHx) can hinder anti-inflammatory phenotype transition of TAMs[95]. Several mechanisms have been proposed to be involved in this process. FAO provides the energy and metabolic intermediates needed for TAMs to suppress anti-tumor T cell activity (e.g., through arginase production, PD-L1 expression, and the secretion of cytokines, such as IL-10), thus inhibiting the immune function of T cell. In contrast, JAK1 functions as an activator of pro-inflammatory signals, whereas SHP-1 acts as a negative regulator to prevent excessive activation. The opposing actions converge within the JAK–STAT pathway to fine-tune macrophage activity[2]. In this context, elevated FAO contributes to the promotion of mitochondrial OXPHOS, production of reactive oxygen species, phosphorylation of JAK1, and dephosphorylation of src homology region 2 domain-containing phosphatase 1, leading to STAT6 activation and transcription of genes (especially *C-C Motif Chemokine Ligand 2* and *Arg1*) that regulate TAM generation and function[21]. Furthermore, several studies have revealed that the scavenger receptor, CD36, has a vital role in the macrophage transition to a more pro-tumoral state. For example, lipid-loaded vesicles are absorbed by macrophages *via* CD36. Genetic ablation of CD36 in these macrophages using *LyzM*-Cre mice resulted in decreased expression of the M2-like marker, CD206, and a concomitant increase in the M1-like marker, CD80. This shift was associated with the activation of $CD8^+$ T cells and the attenuation of liver metastasis[40,96]. Interestingly, CD36 does not affect the CCL2 level, a chemoattractant produced by cancer cells for MDMs but influences how these macrophages react to CCL2. Mechanistically, the myeloid cells highly express p110γ. CD36 alters the sphingolipid composition of lipid rafts, promoting activation of the lipid raft-dependent PI3K catalytic subunit, p110γ. This effect leads to a heightened response to the CCL2/C-C chemokine receptor type 2 chemotactic signal from tumor cells. The use of p110γ inhibitors in mouse models of liver metastasis can inhibit monocyte infiltration, restore anti-tumor immunity, and eliminate the effects of CD36 deficiency on the TME[96]. Nian et al.[97] reported that cancer stem cells (CSCs) establish an IL-34-orchestrated niche to promote tumorigenesis in p53-inactivated liver cancer. The authors discovered that p53 inactivation in tumors induces IL-34 secretion, after which IL-34 upregulates CD36 in TAMs, enhancing lipid uptake and switching metabolism to FAO. This process drives TAMs towards a foam-like, M2-like phenotype. These reprogrammed TAMs are necessary and sufficient to suppress $CD8^+$ T cells, enabling the tumor to escape immune surveillance. Targeting the IL-34-CD36 axis disrupts this pathway, overcomes immune escape, and inhibits tumor growth, particularly in p53-deficient cancers. This finding identified the IL-34-CD36 axis as a crucial mechanism and therapeutic vulnerability for immune-evasive cancers with p53 mutations[97].

The alternatively-activated state of TAMs is usually induced by IL-4. Notably, membrane cholesterol efflux in TAMs is increased in a mouse model of metastatic ovarian cancer, thus promoting IL-4-induced pro-tumor TAM reprogramming in a STAT6/PI3K-dependent manner[98]. When cholesterol-using agents, such as apolipoprotein A1 (ApoA1) were depleted or macrophages were treated with conditioned medium from ID8 cells, the lipid density decreased. This effect was accompanied by a reduction in IFN-γ-induced *Nos2* expression and an increase in the expression of the M2-like marker, *Arg1*. However, Wang et al.[25] identified a positive correlation between cholesterol levels and "do not eat me" signaling in MDMs. The work in GBM revealed that increasing cholesterol efflux *via* the transporter, APOA1, can reinstate macrophage phagocytosis and restore anti-tumor immunity mediated by macrophages and T cells. The dual role of cholesterol efflux highlights the importance of tumor-specific metabolic targeting in immunotherapy. Several lipids have been identified as key regulators of TAM function in the TME. For example, the TME often shows elevated 25-hydroxycholesterol (25-HC) levels. This oxysterol, often produced during inflammation or infection, actively drives TAMs towards an immunosuppressive phenotype and contributes to cold tumors[99,100]. The underlying mechanism has been elucidated recently. A cholesterol-25-hydroxylase (CH25H)-high subset of macrophages is enriched among immunosuppressive TAMs. Lysosome-accumulated 25-HC competes with cholesterol for binding to G protein-coupled receptor 155, thereby inhibiting the kinase mTORC1 and activating the energy sensor, AMPK. Activated AMPK orchestrates a metabolic shift in TAMs, specifically promoting OXPHOS and reducing glycolysis. This metabolic switch is essential for 25-HC to educate macrophages in a STAT6-dependent manner, providing a mechanistic link between cholesterol metabolism, cellular energy sensing, and immune evasion, particularly in colorectal cancer[101]. In addition to cholesterol, AA and its metabolic product, PGE_2, have been well-documented as immunomodulators that educate macrophages in the TME. Hammoud et al. specifically revealed a non-metabolic function of AA within the ovarian cancer immune microenvironment. The study showed that AA acts as an adverse mediator of JAK-STAT signalling in immunosuppressive TAMs by displacing key signalling proteins, including IFNAR1, STAT1, and JAK1, out of cholesterol-enriched lipid raft microdomains, thus promoting an immunosuppressive niche that facilitates tumor progression[102]. Another study highlighted the crucial role of AA in SLC3A2-mediated macrophage polarization in lung adenocarcinoma[103]. PGE_2 activates downstream signaling pathways, including the PI3K–AKT and MAPK signaling pathways, *via* its receptors, such as E-type prostanoid receptor (EP) 2/4, thereby modulating macrophage function. Notably, PGE_2 can profoundly alter mitochondrial activity in macrophages. For

example, in IL-4-induced macrophages, PGE_2 downregulates key genes involved in the malate–aspartate shuttle. This reduction leads to a decrease in mitochondrial membrane potential, which in turn triggers a cascade of changes in nuclear gene expression and ultimately regulates cellular function[104]. As an important immunosuppressive mediator in the TME, PGE_2-EP/EP4 signalling impairs both innate and adaptive immunity in TME. For example, a distinct subset of TAMs in pancreatic ductal adenocarcinoma (PDAC) tumor samples expressing high levels of IL-1β is correlated with poor prognosis. Activated PDAC cells produce more PGE_2 and TNF-α, reinforcing IL-$1\beta^+$ TAM differentiation and IL-1β from TAMs further activate PDAC cells to produce more PGE_2 (*via* prostaglandin-endoperoxide synthase 2/Cyclooxygenase-2) and TNF-α, resulting in a self-reinforcing cycle[105]. In addition, PGE_2 is well-established as an inhibitor of OXPHOS in macrophages, particularly M1-like macrophages. Recently, PGE_2 treatment was reported to suppress OXPHOS and ribosomal protein (RP) biogenesis *via* suppression of peroxisome proliferator-activated receptor gamma coactivator 1α and cell myelocytomatosis oncogene signaling in macrophages. EP4 receptor expression is elevated in activated macrophages, and when present, PGE_2 acts predominantly through this receptor to suppress the pro-inflammatory activity of M1-like macrophages in the TME[106]. Cilenti et al. unravelled a PGE_2-mediated pathway that fine-tunes inflammatory responses in macrophages, which present a transcriptional circuit for IFN-I induction relevant to cancer. PGE_2 interferes with the LPS-mediated activation of extracellular signal-regulated kinase 5, a kinase that acts as a transcriptional partner of myocyte-specific enhancer factor 2A (MEF2A). This disruption prevents ERK5 from phosphorylating/activating MEF2A, thereby dampening IFN-I responses. Consequently, reduced IFN-β leads to diminished expression of a series of pro-inflammatory genes[107]. This evidence supports an immunosuppressive function of PGE_2, especially in response to the pro-inflammatory stimuli in the TME. Similarly, fatty acid and triglyceride metabolism appear to be mechanistically crucial in the functional transition of TAMs[108]. TAMs influence tumor progression by modulating other cellular components within the TME through the secretion of PGE_2. As previously reported, M2-like macrophages promote the differentiation of immunosuppressive cells, such as regulatory T cells (Tregs) and regulatory B cells (Bregs)[109]. $CD169^+$ resident TAMs from lymph nodes, which have been associated with a favorable prognosis in breast cancer patients, significantly inhibited the proliferation of T cells, resting B cells, and NK cells in *in vitro* co-culture experiments. Conversely, $CD169^+$ resident TAMs from lymph nodes markedly enhanced the antibody-producing capacity of activated B cells. These effects were linked to soluble mediators secreted by TAMs, including PGE_2 and IL-10[110]. Sphingolipid metabolism has recently emerged as a key process that links obesity, chronic inflammation, and breast cancer progression by polarizing macrophages toward pro-inflammatory phenotypes and recruiting TAMs to establish a metastasis-favoring TME[111]. LPS/TLR4 activation induces *de novo* sphingolipid synthesis and this metabolic shift is distinct between pro- and anti-inflammatory macrophages. Specifically, sphinganine physically interacts with the TLR4 adaptor proteins, myeloid differentiation primary response 88 and TIR domain containing adaptor protein, facilitating recruitment to the cell membrane after TLR4 activation by LPS. This interaction is essential for initiating downstream NF-κB signalling and pro-inflammatory cytokine production. Inhibition of *de novo* sphingolipid synthesis, and thus sphinganine production in macrophages has been shown to impair the ability to recognize tumor-derived factors *via* pattern recognition receptors, such as TLRs. This impairment hinders the potential to switch towards a more anti-tumor state in melanoma mouse models[112]. As the central intermediate in sphingolipid metabolism, ceramide in TAMs is essential for lipid droplet induction and fatty acid catabolism. Sun et al. reported that the expression of neutral ceramidase (nCDase) is significantly upregulated in TAMs within breast cancer. nCDase hydrolyzes ceramide into sphingosine, which is then phosphorylated to sphingosine-1-phosphate (S1P). This enzymatic activity shifts the sphingolipid balance in TAMs. By conditionally knocking out nCDase in macrophages or supplementing the culture medium with ceramide, the nCDase-S1P axis was shown to promote the differentiation and accumulation of a specific immunosuppressive triggering receptor expressed on the myeloid cells-2 $(TREM2)^+$ TAM subset. These $TREM2^+$ macrophages, known for pro-tumor functions, drive breast cancer progression by inducing $CD8^+$ T cell exhaustion[113]. Within the TME, cancer-associated fibroblasts (CAFs) have an initiating role by "educating" and activating TAMs. This crosstalk is mediated through CAF-secreted C-X-C motif chemokine ligand 12 signaling *via* the C-X-C motif chemokine receptor 4 on TAMs. Activation by CAFs induces marked lipid metabolism reprogramming in $TREM2^+$ lipid-associated macrophages (LAMs). The consequent immunosuppressive milieu further reinforces CAF activation, establishing a feed-forward loop that accelerates tumor progression. Supporting this, animal experiments in the study by Cao et al. demonstrate that the concurrent presence of CAFs and $TREM2^+$ LAMs exerts robust tumor-promoting effect, driving both primary gastic tumor growth and lung metastasis[114]. **Figure 3** summarizes the lipid metabolism-associated signaling pathways in TAMs.

Amino acid metabolism

TAMs utilize amino acid metabolism to directly support an immunosuppressive state within the TME by consuming key amino acids, producing immunosuppressive metabolites, and interacting with tumor cell metabolism[15]. For example, glutamine is suggested to drive the M2-like phenotype in macrophages[115]. Glutamine-derived metabolites, e.g.,

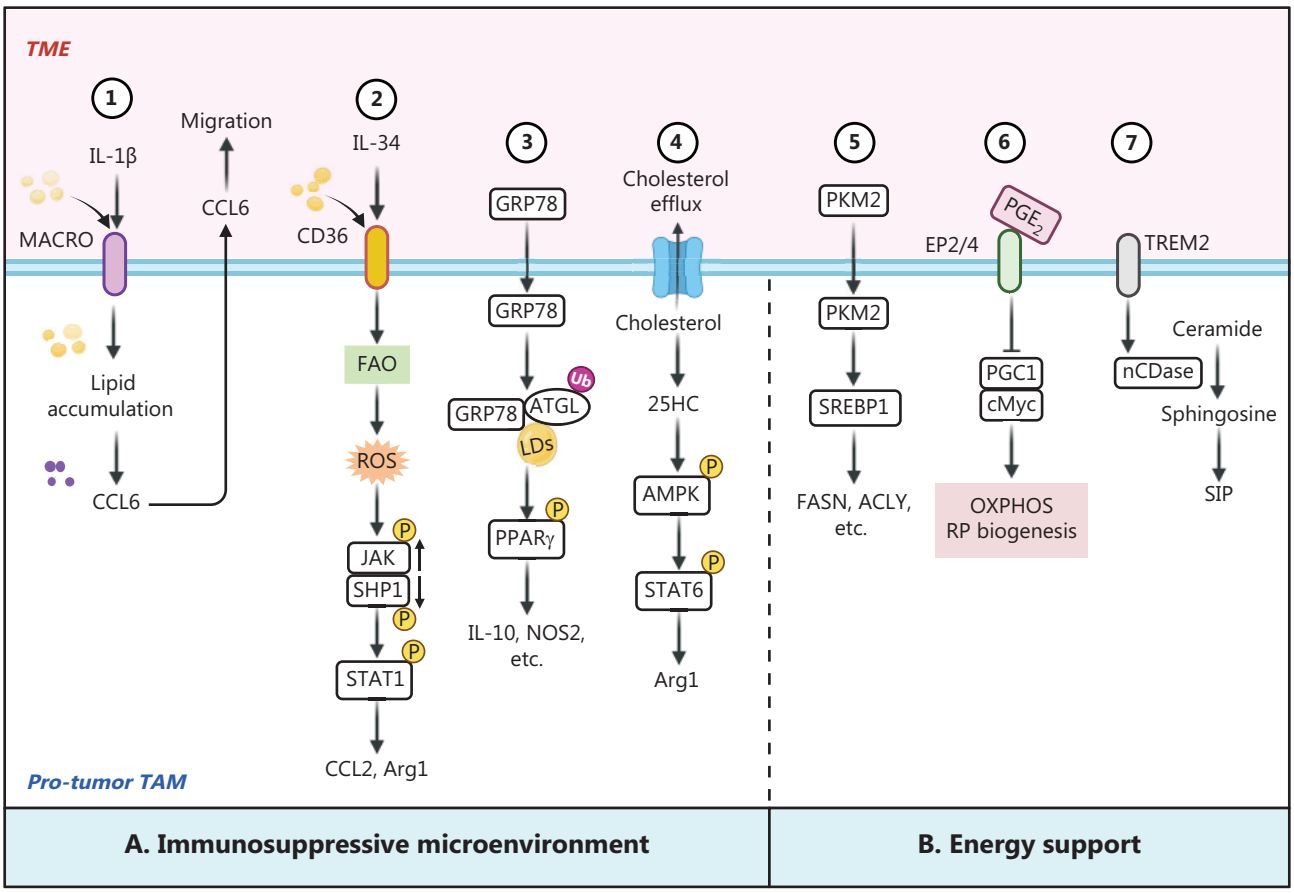


Figure 3 Lipid metabolic rewiring enhances the pro-tumor potential of TAMs. Reprogramming of lipid metabolism in TAMs provides metabolic support and reshapes the TME into an immunosuppressive niche. (A) **Reshape immunosuppressive microenvironment:** ① TAM takes up lipids in response to IL-1β *via* receptor MACRO and the lipid-loaded TAMs produce and release CCL6 to facilitate tumor cell migration; ② In response to IL-34, TAM uptakes lipids *via* the receptor CD36. These lipids subsequently fuel FAO, which in turn enhances the expression of immunosuppressive genes through activation of the JAK-STAT signalling pathway; ③ GRP78 enters macrophages and localizes to LDs, triggering anti-inflammatory gene expression; ④ Cholesterol efflux also drives TAMs toward a pro-tumor state. The enzyme, CH25H, which is enriched in TAMs, catalyzes the conversion of cholesterol to 25-HC. This potent signalling molecule induces pro-tumor macrophage polarization through an AMPK-STAT6-independent mechanism. (B) **Energy support for pro-tumor TAMs:** ⑤ Exosomal PKM2 increases the nuclear accumulation of SREBP1, upregulating fatty acid synthesis; ⑥ Within the TME, PGE_2 derived from malignant cells binds to EP2 and EP4 receptors on TAMs. This binding suppresses OXPHOS and ribosome biogenesis, thereby impairing M1-like macrophage polarization; ⑦ Furthermore, the nCDase-S1P axis maintains sphingolipid homeostasis in TAMs to support pro-tumor functions. ACLY, ATP-citrate lyase; AMPK, AMP-activated protein kinase; Arg1, arginase-1; ATGL, adipose triglyceride lipase; CH25H, cholesterol-25-hydroxylase; EP2/4, E-type prostanoid receptor 2/4; FASN, fatty acid synthase; JAK, janus kinase; LDs, lipid droplets; MACRO, macrophage receptor with collagenous structure; NOS2, nitric oxide synthase 2; OXPHOS, oxidative phosphorylation; PGE_2, prostaglandin E2; PGC1, peroxisome proliferator-activated receptor γ coactivator 1-α; PKM2, pyruvate kinase isozyme type M2; PPARγ, peroxisome proliferator-activated receptor γ; RP, ribosomal protein; SHP1, Src homology region 2 domain-containing phosphatase-1; SIP, sphingosine-1-phosphate; TREM2, triggering receptor expressed on myeloid cells 2; TME, tumor microenvironment; Ub: ubiquitination. CCL6, Chemokine (C-C motif) ligand 6; FAO, Fatty acid oxidation; ROS Reactive oxygen species; STAT1, Signal transducer and activator of transcription 1; STAT6, Signal transducer and activator of transcription 6; GRP78, Glucose-regulated protein 78; SREBP1, Sterol regulatory element-binding protein 1; cMyc, Cellular myelocytomatosis oncogene; nCDase, Neutral ceramidase; TAM, Tumor-associated macrophages.

α-ketoglutarate, succinate, and aspartate, are identified as critical regulators of macrophage functions through metabolic and epigenetic reprogramming[116]. Orillion et al. reported that amino acid deprivation suppresses TAM infiltration and tumor growth, while promoting sensitivity to immunotherapies. In the current study dietary amino acid restriction was shown to drive macrophage repolarization to a tumor-suppressive state, characterized by altered cytokine production (e.g., increased

IL-12/TNF-α and decreased IL-10) and enhanced phagocytosis *via* the ROS-mTOR cascade[117]. In addition, CAFs synthesize and release glutamine, which is subsequently taken up by TAMs. This uptake promotes the polarization of TAMs towards a pro-tumor phenotype, thereby contributing to an immunosuppressive TME and supporting tumor growth. Importantly, CRISPR/Cas9-mediated knockdown of glutamine synthesis (GS) in CAFs significantly impaired the capacity to induce macrophage polarization, demonstrating that the glutamine-producing function of CAFs is critical for driving this process[118].

Enhanced glutamine metabolism has been implicated as an important switch that governs TAM polarization within the TME. GS expression and activity are induced by anti-inflammatory stimuli within the TME, especially under starvation, and GS abrogation makes macrophages reliant on extracellular glutamine uptake, which activates the mTORC1 signalling pathway, thus resulting in macrophage reprogramming towards an M1-like phenotype[119]. Macrophages in myeloid-rich prostate and bladder cancers (known as immunologically 'cold' and myeloid-rich tumors) treated with the glutamine antagonist, JHU083, or reprogrammed macrophages exhibited increased glycolysis, disrupted TCA cycle, and disrupted purine metabolism. Moreover, in addition to pro-tumor polarization, this metabolic rewiring might promote phagocytosis *via* myosin 1e. The myosin family protein, Myo1E, which is encoded by the gene, *Myo1e*, is essential for adhesion turnover during phagocytosis in macrophages. Myo1E facilitates membrane-cytoskeleton crosstalk to enable phagocytic cup closure[120]. This effect of glutamine metabolism on phenotype skewing exists not only in TAMs but also in other suppressive myeloid cells, such as myeloid-derived suppressor cells (MDSCs)[121]. Recently, Liu et al. demonstrated that CD40 signaling promotes pro-inflammatory macrophage polarization by enhancing FAO and glutamine metabolism in melanoma. First, bone marrow-derived macrophages were treated with the CD40-activating monoclonal antibody, FGK45. This treatment increased the oxygen consumption rate (OCR) and triggered glycolysis in a glucose-independent manner. When OXPHOS was inhibited using rotenone or oligomycin, FGK45-induced M1-like polarization was blocked. Second, using Carnitine palmitoyltransferase 1-deficient mice to inhibit FAO or by knocking out glutaminase 1 (GLS1)/LDHA to disrupt glutamine metabolism, CD40-triggered macrophage polarization was similarly suppressed. Mechanistically, fatty acids are broken down into acetyl-CoA during FAO. Using ^{13}C-labeled palmitate tracer analysis, FGK45 treatment significantly increased the levels of citrate and other TCA cycle metabolites in macrophages. Citrate serves as an acetyl-CoA donor for protein acetylation and epigenetic regulation. Moreover, glutamine acts as a substrate for glycolysis, which in turn fine-tunes the NAD^+:NADH ratio to maintain NAD^+ levels and support FAO. It is now clear that enhanced glycolysis stabilizes HIF-1α, with breakpoints at IDH and SDH in the TCA cycle during LPS-induced pro-inflammatory polarization[122]. Intriguingly, CD40-mediated M1 polarization occurs in an OXPHOS-dependent manner, and notably, the TCA cycle remains intact during this process. CD40-mediated M1 polarization reveals a novel and previously unreported mechanism of metabolic reprogramming underlying macrophage polarization triggered by CD40[123]. Extracellular vesicles (EVs) from tumor cells, particularly microvesicles containing GLS1, is another factor to facilitate glutamine metabolism, then drive the M2-like polarization of TAMs. Hu et al. reported that HER2-positive gastric cancer cells (trastuzumab-resistant) exhibit increased CDC42 expression. Treatment with the CDC42 inhibitor, ZCL278, significantly reduced microvesicle marker protein expression. Mechanistically, CDC42 activated NF-κB p65 to regulate GLS1, promoting GLS1 microvesicle secretion through IQ motif containing GTPase activating protein 1. In co-culture experiments with macrophages, the addition of the GLS1 inhibitors, BPTES or CB839, significantly decreased GLS1 expression in macrophages. This treatment also upregulated M1 macrophage markers and reduced M2 macrophage markers[124]. In addition, glutamine-derived aspartate contributed to the pro-inflammatory phenotype reprogramming of TAMs in HCC. As reported, aspartate upregulates spermidine through the polyamine synthesis pathway. Spermidine facilitates Eukaryotic translation initiation factor 5A hypusination, which contributes to the efficient translation of mRNAs encoding proteins with polyproline motifs, including HIF-1α[125]. Mills et al. revealed that one of the breaks in the Krebs cycle involved in pro-inflammatory macrophage polarization and the increased IL-1β level caused by SDH also requires HIF mRNA translation and stabilization[126].

Immunosuppressive TAMs are characterized by tryptophan metabolism skewing, which is evidenced by enhanced indoleamine 2,3-dioxygenase 1 (IDO1) and/or aryl hydrocarbon receptor (AhR) activity[127]. In a study integrating 178,651 human mononuclear phagocytes from 13 tissues, IL4I1$^+$ MDMs were shown to have a higher level of the *IDO1* gene in tumors than adjacent tissues and exhibit immunosuppressive characteristics[128]. The monocytes gathered at the tumor periphery in a T cell-dependent manner and were matured by IFN-γ (produced *via* IFN-γ signalling and the CD40/CD40L interaction). The matured TAMs then recruit Tregs to tumors through degradation of tryptophan. In addition to TAMs, studies of other tumoral intrinsic components in classic Hodgkin lymphoma (cHL) have demonstrated that mononuclear phagocytes (e.g., cDCs and monocytes) also express immunoregulatory factors, such as PD-L1, T cell immunoglobulin and mucin domain-containing protein 3, and the tryptophan-catabolizing protein, IDO. The TME of cHL exhibits compartmental niches where these phagocytes form dense clusters around malignant cells to facilitate direct cell-cell interactions that promote immune evasion and tumor growth[129]. IDO1 and tryptophan 2,3-dioxygenase (TDO2) mediate tryptophan degradation to produce kynurenine and its derivatives, which activate AhR. However, Sadik et al. showed that Interleukin 4 induced 1 is more strongly and frequently associated with AhR compared to TDO1 or TDO2[130]. In addition, microbiome-produced tryptophan metabolites have recently emerged as activators

of the TAM AhR. TAMs were shown to exhibit higher AhR activity compared to resident macrophages and Ahr-deficient macrophages become pro-inflammatory. Kynurenine alone was verified to be a relatively weak activator of AhR, whereas tryptophan metabolite indoles [e.g., indole, indole-3-aldehyde (IAld), indole-3-acetic acid (IAA), Indole-3-propionic acid (IPA) and Indole-3-lactic acid (ILA)] produced by the gut microbiota (specifically some *Lactobacillus* spp.) act as potent co-agonists with kynurenine to activate TAM AhR far more effectively than either molecule alone. These reprogrammed TAMs highly express canonical M2-like macrophage markers (CD206, IL-10, and VEGF). The reprogrammed TAMs directly suppress the activity of cytotoxic $CD8^+$ T cells within the tumor, thereby promoting PDAC tumor growth[54].

Emerging evidence has demonstrated that serine, an essential amino acid for nucleotide/protein/lipid synthesis, orchestrates macrophage phenotype polarization and/or functional transition, is involved in oncogenesis and progression. The TME increases the activity of the protein kinase RNA-like endoplasmic reticulum kinase (PERK) signalling cascade in TAMs and promotes M2-like TAM activation and proliferation. PERK activation mediates serine biosynthesis *via* the downstream transcription factor, ATF4, a master regulator of amino acid metabolism that increases serine biosynthesis. Furthermore, increased serine enhances mitochondrial function and α-KG production, which are required for Jumonji domain containing-3 (JMJD3)-dependent epigenetic modification. Raines et al. performed an unbiased ChIP-Seq analysis of macrophages that were either PERK-sufficient or -deficient. PERK-deficient (cKO) macrophages showed greater enrichment of regions with increased H3K27 methylation in M2-like macrophages than M1-like macrophages compared to PERK wild-type (WT) macrophages. Specifically, H3K27 methylation was elevated at the loci of canonical M2 genes, including *interferon regulatory factor 4 (Irf4), peroxisome proliferator-activated receptor γ (Pparg)*, and *macrophage galactose-type lectin 2 (Mgl2)*, in PERK-deficient M2-like cells[131]. Mitochondrial dysfunction is a pivotal factor in serine-mediated macrophage education. mtROS stabilize HIF-1α in pro-inflammatory macrophages. HIF-1α is translocated to the nucleus and drives the expression of nuclear respiratory factors nuclear respiratory factor 1 *(NRF1)*/specificity protein 1 *(Sp1)*. These factors activate gene transcription for mitochondrial biogenesis (e.g., Mitochondrial transcription factor a and respiratory chain components), leading to the secretion of inflammatory factors. In contrast, *de novo* serine synthesis hinders this pathway by promoting cytoplasmic glutathione (GSH) synthesis to deprive mtROS *via* phosphoglycerate dehydrogenase (PHGDH), the first enzyme in the serine synthesis pathway[12]. This proposed mechanism in macrophages contrasts with the mechanism in RCC in which HIF-1 negatively regulates mitochondrial biogenesis through repression of C-MYC.

Polyamines are derived from amino acids and are essential nitrogen-containing compounds in cells. Polyamines are synthesized from L-ornithine. The precursor of L-ornithine is arginine, which is acted on by ornithine decarboxylase (ODC, also known as ODC1). Polyamine synthesis causes an increase in the putrescine level, which hinders pro-inflammatory macrophage polarization[132]. Cancer cells and other pro-tumorigenic cell types (e.g., MDSCs, TAMs, and Tregs) are highly dependent on polyamines for survival in a wide variety of cancers. The intra- and extra-cellular polyamine pools of cancer cells increase to support the fundamental cellular processes and functions of TAMs[133]. Arginine levels are downregulated in the pro-tumor TAMs of breast cancer, whereas the levels of the polyamine products (ornithine, putrescine, spermidine, and spermine) are upregulated (upregulated Arg1 depletes arginine and produces ornithine). Mechanistically, spermine upregulates thymine DNA glycosylase (TDG) expression *via* triggering the p53 signalling pathway. This upregulation leads to pro-tumor TAM skewing *via* TDG-mediated DNA demethylation of the target gene, peroxisome-proliferator-activated receptor gamma (*PPARG*). PPARγ activation leads to the transcription of *CD274*, *TGFB1*, and *IL-10*[15].

Studies have demonstrated that amino acid metabolism in B cells regulates the function of TAMs. Zhang et al. used stable isotope tracing with $^{13}C_5$ and $^{15}N_2$-glutamine, and confirmed that, unlike T cells, B cells can convert glutamine into gamma-aminobutyric acid (GABA) and secrete glutamine extracellularly. B-cell-derived GABA was identified as a key mediator suppressing anti-tumor immunity in a CRC mouse model. To explore the underlying mechanism, mouse or human monocytes were treated with GABA, which induced differentiation into macrophages. These macrophages exhibited higher proliferation and survival rates, increased OXPHOS capacity, and elevated expression of folate receptor β (FRβ), a marker associated with an M2-like phenotype. Furthermore, these cells secreted high levels of IL-10, which potently inhibited the cytotoxic function of $CD8^+$ T cells[134]. Amino acid metabolism-related signaling pathways in TAMs are summarized in **Figure 4**.

Other metabolism

Bile acid synthesis occurs primarily in the liver *via* classical and alternative cholesterol pathways. Bile acid modification and transformation are carried out mainly by the gut microbiota in the intestine[135]. Macrophages do not perform classical *de novo* bile acid synthesis, but macrophages can sense, take up, and respond to bile acids and metabolites within the TME, thereby modulating bile acid functions[136]. Cytochrome P450 enzymes, such as CYP7A1 and CYP27A1, act as rate-limiting enzymes in bile acid synthesis. These enzymes are highly expressed in hepatocytes but are nearly absent or expressed minimal in immune cells, such as macrophages[137]. Macrophages express various bile acid receptors on surfaces and intracellularly, including the nuclear receptors, farnesoid X receptor (FXR) and vitamin D receptor (VDR), as well as the membrane receptor, takeda G-protein–receptor 5 (TGR5). For example,

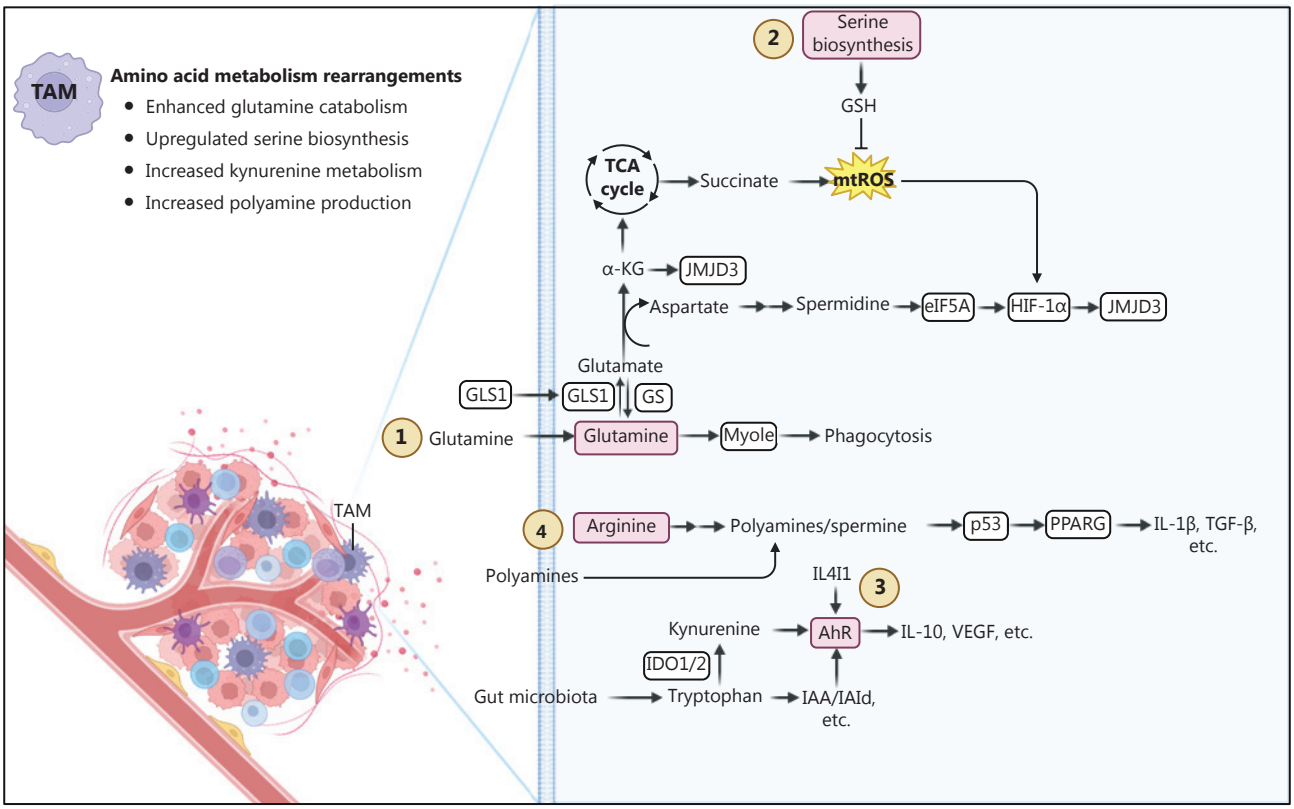


Figure 4 The mechanisms link amino acid metabolic rewiring and TAM functions. Reprogrammed amino acid metabolism underpins the acquisition of an immunosuppressive phenotype in TAMs. TAMs rely on glutamine uptake for phagocytic activity. ① **Enhanced glutamine catabolism:** The enhancement of glutamine catabolism, involving conversion to glutamate, serves as fuel for both spermidine synthesis and the TCA cycle. This process drives the acquisition of immunosuppressive functions; ② **Upregulated serine biosynthesis:** Elevated serine biosynthesis promotes mitochondrial biogenesis *via* glutathione GSH production. This reduces mtROS levels, which otherwise regulates pro-tumor gene expression through HIF-1α and epigenetic mechanisms; ③ **Increased kynurenine metabolism:** During the immunosuppressive transition of TAMs, tryptophan derived from the gut microbiota or *via* IL4I1, accelerates the production of IL-10 and other anti-inflammatory cytokines through AhR activation; ④ **Increased polyamine production:** Arginase-1 depletes arginine to produce polyamines. These endogenous polyamines synergize with excess polyamines from the TME to engage the p53 signalling pathway, further elevating levels of immunosuppressive factors, such as IL-1β. AhR, aryl hydrocarbon receptor; eIF5A, eukaryotic translation initiation factor 5A; GLS1, glutaminase 1; GS, glutamine synthetase; GSH, glutathione; HIF-1α, hypoxia-inducible factor 1; IAA, indole-3-acetic acid; IAId, indole-3-aldehyde; IDO, indoleamine 2,3-dioxygenase; JMJD3, Jumonji domain containing-3; PPARG, peroxisome-proliferator-activated receptor gamma; VEGF, vascular endothelial growth factor; α-KG, α-ketoglutaric acid. TAM, Tumor-Associated Macrophages; mtROS : Mitochondrial Reactive Oxygen Species; TCA, Tricarboxylic Acid Cycle; IL4I1, Interleukin-4 Induced Gene 1; TGF-β : Transforming Growth Factor β.

deoxycholic acid can act through the TGR5 signaling pathway to reduce the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12p70, and TNF-α, by macrophages, thereby exerting anti-inflammatory effects[138]. Sirtuin 5 has a critical role in a Yap5SA-driven mouse model of liver cancer. Excessive succinylation of the peroxisomal enzyme, acyl-coa oxidase 2 (ACOX2), leads to activation of the bile acid synthesis pathway in Sirt5-deficient hepatocytes and increased production of taurocholic acid (T-CA). T-CA promotes the polarization of M2-like TAMs through paracrine signaling, which in turn drives liver cancer progression[139].

Iron is an essential cofactor for key proteins, such as cytochromes, in the mitochondrial electron transport chain (ETC). Tumor cells typically exhibit extremely high iron requirements to support proliferation, DNA synthesis, and energy metabolism[140]. To meet this demand, tumor cells hijack iron by upregulating transferrin receptor 1 (TFR1), creating a relatively iron-deficient and hypoxic state within the TME, particularly in the tumor core. Decreased intracellular iron levels or damage to iron-sulfur clusters can impair the antibacterial and anti-tumor functions of M1 macrophages. Cancer cells compete with macrophages in HCC for iron by overexpressing transferrin receptor (TFRC). Analyses of human and mouse HCC samples have shown that ferrous ion levels are significantly lower in M2-like TAMs than M1 counterparts. Furthermore, treating

macrophages with iron chelators, such as deferasirox (DFX) or ciclopirox (CPX), upregulates the levels of M2 marker gene expression (e.g., *Arg1*, *Vegfa*, and *PD-L1*) and suppresses T cell proliferation[59]. $CD63^+$ macrophage subsets constitute a key immunomodulatory node in the bone metastasis microenvironment with the immunosuppressive function being directly attributable to aberrant iron metabolism. Therapeutic application of a CD63-targeted nanosystem loaded with a ferroptosis inducer in a mouse model of bone metastasis promoted the infiltration of M1-like TAMs and cytotoxic $CD8^+$ T cells into the TME and significantly reduced the bone metastasis burden[141].

Immunotherapy targeting TAM

There are several therapeutic strategies targeting TAMs: the synergistic combination of TAM "reprogramming" and functional "reactivation"; and integration of these modalities with conventional therapies. The metabolic reprogramming of TAMs promotes tumor progression and immune evasion, making TAMs compelling targets for new anticancer drugs. Thus, the exploration of TAM-specific metabolic targets has revealed a novel paradigm for therapeutic intervention. This summary explores immunotherapies developed to target TAMs with the current opportunities and challenges in this field (**Figure 5**).

TAM reduction

The core mechanism involves TAMs being "domesticated" by tumor cells to act as accomplices in promoting cancer. Extensive research has revealed that a high abundance of TAMs is strongly linked to poor patient prognosis across many cancer types[142]. Thus, strategies to reduce TAM infiltration in the TME remain among the most extensively studied approaches. For example, blocking CSF-1R, which is primarily expressed on TAMs, suppresses TAM survival. Inhibiting the CCL2/CCR2 axis directly reduces monocyte recruitment to the TME. Furthermore, clodronate liposomes, including the novel Clo-Lipo-DOTAP formulation, have been shown to effectively deplete TAMs by inducing apoptosis *via* phagocytosis in melanoma and colon cancer models[143]. This approach further validates the strategy of TAM depletion, although it has thus far been applied primarily in preclinical mouse models. Current monotherapy approaches aimed at reducing the number of TAMs face significant limitations. These limitations include side effects, such as neutropenia

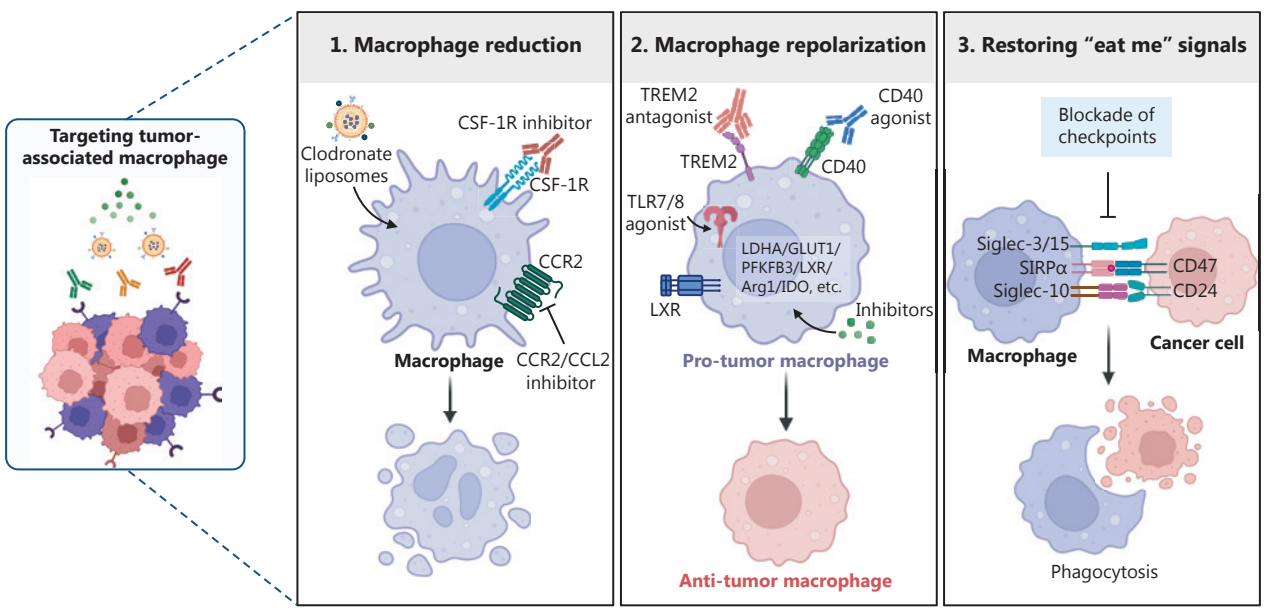


Figure 5 Therapeutic strategies targeting TAMs. Currently, three primary strategies have been developed to target TAMs, aiming to achieve greater efficacy in tumor treatment. **1. TAM reduction:** CSF-1R or CCR2/CCL2 inhibitors that block CSF-1R and CCR2/CCL2 axis to reduce the number of TAMs. In addition, clodronate liposomes induce apoptosis of TAMs, further decreasing abundance in the tumor microenvironment; **2. TAM repolarization:** TLR7/8 agonists, CD40 agonists, and TREM2 antagonists can reprogram TAMs from a pro-tumor phenotype to an anti-tumor phenotype. Several metabolic targets, including LDHA, GLUT1, PFKFB3, LXR, Arg1, and IDO have shown potential for reshaping TAM phenotype and thereby modulating tumor progression; **3. Restoring "eat me" signals:** Blocking the immune checkpoints, such as CD47-SIRPα, CD24-Siglec-10, and Siglec-3/15, can restore "eat me" signals and promote the phagocytic activity of TAMs against cancer cells. CCL2, C-C chemokine ligand 2; CCR2, C-C chemokine receptor type 2; CSF-1R, colony-stimulating factor 1 receptor; TLR7/8, Toll-like receptor 7/8; TREM2, triggering receptor expressed on myeloid cells 2. LXR, Liver X Receptor; LDHA, Lactate Dehydrogenase A; GLUT1 – Glucose Transporter 1; PFKFB3, 6-Phosphofructo-2-Kinase/Fructose-2,6-Bisphosphatase 3; Arg1, Arginase 1; SIRPα – Signal Regulatory Protein α.

and thrombocytopenia, as well as low response rates in solid tumors. Chen et al. demonstrated that the CSF1R inhibitors (BLZ945 and PLX3397) alone had only a modest anti-tumor effect on head and neck squamous cell carcinoma (HNSCC). However, when combined with cisplatin, CSF1R inhibitors significantly suppressed tumor progression compared to monotherapy[144]. Targeting the CCL2/CCR2 axis is another approach to reduce monocyte/macrophage numbers in the TME. However, this approach typically induces only a transient reduction because the approach is counteracted by a compensatory increase in CXCL1/3. Given these limitations, combination therapies have shown superior efficacy to monotherapy. These strategies extend beyond combinations with anti-PD-1[145]. For instance, a recent study used a vascularized tumor tissue model to evaluate a multispecific antibody targeting CCR2, CSF-1R, and TGF-β, which successfully reduced monocyte levels[146]. These findings indicated that an approach to deplete TAMs holds promise as part of combination therapy for specific cancers.

TAM repolarization

A more promising approach to circumvent the side effects associated with depleting monocytic TAMs is to repolarize TAMs within the TME, thereby improving therapeutic efficacy. CD40 signaling initiates metabolic reprogramming characterized by enhanced FAO and glutamine metabolism. These pathways provide substrates for ACLY, culminating in ACLY-dependent epigenetic remodeling. CD40 agonists effectively repolarize immunosuppressive M2-like TAMs toward an immunostimulatory M1-like state through this mechanism. This transition enhances antigen presentation and promotes the infiltration of $CD8^+$ T cells into the TME[123]. Nevertheless, the efficacy of CD40 agonism as monotherapy is limited and systemic activation often leads to significant toxicity. To address this finding, strategies using engineered antibodies and refined administration methods are being developed to enhance targeting of tumor or TAM[147]. Concurrently, combination therapy with immune checkpoint inhibitors has emerged as the most common clinical strategy to maximize benefit. TREM2, a core hub for lipid metabolism regulation, has emerged as a promising new target for reprogramming the TME through TAMs with targets, such as CD40. TREM2 engages with multiple ligands, activating context-dependent signaling pathways that influence disease progression[148]. Inhibiting TREM2 to disrupt immunosuppressive networks has shown therapeutic potential in oncology, albeit with outcomes that vary across cancer types. Monoclonal antibodies and chimeric antigen receptor macrophages (CAR-Ms) are currently under investigation in preclinical and early clinical development. The Amit laboratory (Weizmann Institute of Science, Rehovot, Israel) recently developed myeloid-targeted immunocytokines and NK/T-cell enhancers (MiTEs), a novel antibody-based therapy that depletes $TREM2^+$ TAMs and acts in a tumor-restricted manner to enhance killer cell cytotoxicity[149]. This finding represents a remarkable discovery in which immune cells are reprogrammed to kill tumors.

The broad distribution of macrophages complicates TAMs targeting because there is a risk of off-target effects and systemic immune dysregulation. Elevated IRG1 expression in TAMs triggers M2-like polarization, making IRG1 a promising cancer target. Recently, the Yang laboratory (Huazhong University of Science and Technology, Wuhan, China) designed a lipid nanoparticle (LNP) encapsulating siRNA to effectively silence Irg1 in TAMs[150]. This strategy demonstrated potent anti-tumor efficacy and favorable safety profiles in melanoma and colon cancer models. The mechanisms by which succinate modulates TAM polarization have been characterized and SMPs exhibit improved anticancer immunotherapy effects, establishing succinate as a viable oncologic target. A central challenge in leveraging this target is the efficient intracellular delivery of succinate into macrophages, circumventing an interaction with the surface receptor, SUCNR1. To overcome this membrane barrier, the Tang laboratory (Huazhong University of Science and Technology, Wuhan, China) developed novel microparticles to deliver high concentrations of succinate directly into the cellular interior[37]. Furthermore, macrophage-specific folate receptor β (FR-β, encoded by *folr2*) is a validated cancer target that is highly expressed on TAMs. The Wang laboratory (Hebei Medical University, Shijiazhuang, China) has developed an FR-β–targeting chimeric molecule that repolarizes TAMs to an M1-like state in the TME. By linking the TLR7/8 agonist, IMDQ (a reprogramming agent lacking specificity) to a 6-substituted pyrrolo[2,3-d]pyrimidine, the construct achieves higher affinity for FR-β than folate does and demonstrates applicability across multiple cancer types[151].

The core of therapeutic strategies targeting CD36 on TAMs involves disrupting reprogrammed lipid metabolism. This intervention aimed to reverse the protumor M2-like polarization and alleviated suppression of anti-tumor immunity. One of the earliest and most extensively studied CD36 inhibitors is sulfonyl-N-succinimide oleate (SSO). For example, Xu et al.[152] demonstrated that oxidized low-density lipoprotein (oxLDL) activates p38 signaling to suppress IFN-I production in mouse and human macrophages. Blocking CD36 with SSO inhibits this process and has been shown to be effective in melanoma and CRC mouse models. Recent studies have indicated that CD36 expression is elevated in metastasis-associated macrophages isolated from metastatic liver tumors. Sheue-Fen et al. developed a humanized anti-CD36 monoclonal antibody (PLT012). By targeting metabolic pathways, PLT012 can remodel the immune microenvironment in HCC and liver metastases, affecting TAMs, $CD8^+$ T cells, and NK cells, and thereby restoring anti-tumor immunity. This approach holds potential for future immunotherapy in liver cancer[153]. In summary, most anti-tumor strategies directed at CD36 remain in preclinical or early-stage clinical (phase I/II) development, with no therapies formally approved for clinical use. Importantly, CD36 is also expressed on various normal

Table 1 Summary of cancer therapies targeting TAM

Target	Agent	Tumor type	Implications for TAMs	Clinical trial number
CSF-1R	CSF-1R inhibitor		TAMs reduction	
	BLZ945	Advanced solid tumors		NCT02829723 NCT02526017
	PLX3397	Giant cell tumor of tendinous sheath Advanced solid cancer		NCT02371369[159] NCT02734433[160]
CCL2/CCR2	Anti-CCL2		TAMs reduction	
	CNTO 888	Metastatic pancreatic cancer		NCT00992186
	PF-04136309	Metastatic pancreatic ductal adenocarcinoma		NCT02732938[161]
	CCR2 inhibitor	Pancreatic cancer		
	CCX872-B			NCT02345408
	Clo-Lipo-DOTAP	-	TAMs reduction	Preclinical study[143]
CD40	CD40 agonist	Metastatic solid cancer	TAMs repolarization	
	CP-870893	Advanced cancer		NCT01103635
	SEA-CD40	Advanced solid cancer		NCT02376699[162]
	ChiLob7/4	Pancreatic cancer		NCT01561911[163]
	APX005M			NCT03597282
TREM2	TREM2 inhibitors	Advanced solid cancer	TAMs repolarization	NCT04691375[164]
	PY314			
IRG1	Lipid nanoparticle encapsulating siRNA	-	TAMs repolarization	Preclinical study[150]
Metabolism			TAMs repolarization	
GLUT1	WZB117	-		Preclinical study[165]
PFKFB3	3PO	-		Preclinical study[166]
LXR	GW3965	-		Preclinical study[167]
FABP5	SBFI-26	-		Preclinical study[168]
Glutaminase	JHU083	-		Preclinical study[169]
Arg1	CB-1158*	Solid cancer		NCT02903914
IDO	Epacadostat	Melanoma		NCT02178722
CD47-SIRPα	Anti-CD47		TAM repolarization	
	Hu5F9-G4	Acute myeloid leukemia		NCT02216409[170]
	SRF231	Advanced solid cancers/Hematologic cancers		NCT03512340
	ALX148	Acute myeloid leukemia		NCT03013218[171]
	Anti-CD47/SIRPα			
	HCB101			Preclinical study[155]
CD24-Siglec10	PHST001	Advanced solid cancer	Restoring “eat me” signals	NCT06840886

Table 1 Continued

Target	Agent	Tumor type	Implications for TAMs	Clinical trial number
	IMM47	Advanced solid cancer		NCT05985083
	ATG-031	Advanced solid cancer/B-cell non-Hodgkin's lymphoma		NCT06028373
Siglec-3 (CD33)	Mylotarg*	Acute myeloid leukemia	Restoring "eat me" signals	NCT00372593[172] NCT05189639 NCT01698879
Siglec-15	NC318	Advanced solid cancer	Restoring "eat me" signals	NCT03665285
Neu2 Fc fusion protein	E-602	Advanced solid cancer	Restoring "eat me" signals	NCT05259696

Drugs marked with an asterisk (*) are FDA-approved. ARG1, arginase 1; CCL2, C-C chemokine ligand 2; CCR2, C-C chemokine receptor type 2; CD24-Siglec10, CD24–sialic acid-binding Ig-like lectin 10; CD47-SIRPα, CD47-signal regulatory protein alpha; CSF-1R, colony-stimulating factor 1 receptor; FABP5, fatty acid-binding protein 5; GLUT1, glucose transporter type 1; IDO, indoleamine 2,3-dioxygenase; IRG1, immune-responsive gene 1; LXR, liver X receptor; NCT, National Clinical Trial (ClinicalTrials.gov identifier); PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; Siglec-3, sialic acid-binding Ig-like lectin 3; Siglec-15, sialic acid-binding Ig-like lectin 15; TAMs, tumor-associated macrophages; TREM2, triggering receptor expressed on myeloid cells 2.

cell types, including endothelial cells, platelets, and muscle cells. Consequently, potential systemic side effects, such as an impact on angiogenesis and systemic energy metabolism, as well as off-target effects, require careful consideration. In addition, inhibiting CD36 expression may drive TAMs to acquire fatty acids through alternative pathways, potentially leading to drug resistance. Addressing this adaptive response remains a key challenge in the development of CD36-targeted therapies.

Therapeutic small molecules targeting metabolic enzymes have been shown to alter the TAM phenotype and tumor progression. For example, energy deprivation can be achieved with the GLUT1 inhibitor, WZB117, whereas PD-L1 expression is downregulated by the PFKFB3 inhibitor, 3PO. Inhibiting LDHA with oxamate suppresses OXPHOS and promotes repolarization toward an M1-like phenotype. Reprogramming lipid metabolism *via* the LXR agonist, GW3965, or the FABP5 inhibitor, SBFI-26, reduces the population of protumor TAMs. Similarly, research has confirmed the effectiveness of the glutaminase inhibitor, JHU083, and the Arg1 inhibitor, CB-1158[154]. Most of these small molecules have exhibited potential in preclinical studies. However, translation to clinical success is not guaranteed. A case in point is the IDO inhibitor, epacadostat, which demonstrated excellent anticancer efficacy in earlier research but ultimately met with setbacks in a phase III clinical trial. Moreover, the development of these metabolic immunotherapy approaches is significantly hampered by the persistent challenge of effectively targeting TAMs.

Restoring "eat me" signals

The phagocytosis of tumor antigens and direct clearance of cancer cells are critical functions of macrophages. However, this activity is highly suppressed within the TME and even systemically suppressed due to the abundance of immunosuppressive signals. The interaction between inhibitory ligands expressed by tumor cells and receptors on TAMs activates suppressive intracellular signals. This interaction leads to the repression of phagocytosis and promotion of immune evasion. Among these intracellular signsl, "do not eat me" signals are the most significant inhibitory component. Preclinical and early-stage clinical trials have indicated that blocking these inhibitory phagocytic checkpoints or restoring "eat me" signals represents a promising therapeutic strategy for cancer.

The CD47–SIRPα signaling axis is a dominant "do not eat me" signaling pathway that protects cells, including cancer cells, from phagocytic clearance. Early anti-CD47 therapies induce severe blood toxicity because CD47 is ubiquitously expressed on cancer cells and red blood cells (RBCs). Current next-generation agents, such as the Fc-fusion-mutant SIRPα protein, HCB101, are engineered to bind CD47 on cancer cells with high affinity, while exhibiting minimal binding to RBCs[155]. A major challenge in therapeutic strategies targeting the CD47–SIRPα checkpoint is the compensatory triggering of the CD24–Siglec-10 axis, another prominent "do not eat me" signal that contributes to cancer immune evasion. Anti-CD24 and the anti-CD24/anti-CD47 combination induced higher phagocytic activity against ovarian cancer cells than anti-CD47 alone. Thus, targeting the CD24–Siglec10 axis has become a rapidly developing strategy and several monoclonal anti-CD24 antibodies are currently in clinical trials, e.g., PHST001, IMM47 and ATG-031 (ClinicalTrials.gov). In addition, Zhang et al. developed an implantable microneedle device for surgical cavity placement to prevent postoperative tumor recurrence. The microneedle delivers macrophage-activating nanoparticles (GMANs), which block the CD24–Siglec10 "do not eat me" signaling pathway, thereby enhancing macrophage

recognition and phagocytosis of tumor cells[156]. Concurrently, the GMANs inhibit the expression of oncostatin M (OSM), helping to reverse postoperative immunosuppression within the TME. Furthermore, the microneedle is conjugated with the immune adjuvant CpG oligonucleotide to recruit immune cells to the site and generate a localized anti-tumor immune response. Although CD24–Siglec10 blockade has a superior blood safety profile compared to CD47 blockade, studies have indicated that CD24–Siglec10 blockade may compensate for activation of the CD47–SIRPα pathway. Future therapies may combine these monoclonal antibodies with CAR-M and/or other targeted agents.

Tumor cells can achieve immune evasion by overexpressing glycans modified with sialic acid (SA). Siglecs, the primary receptors for SA, are expressed predominantly on immune cell surfaces. Binding to SA ligands transmits positive or negative regulatory signals into cells, thereby actively modulating innate and adaptive immune responses[157]. Therapeutically, several monoclonal antibodies have been developed to target Siglecs. For example, gemtuzumab ozogamicin (Mylotarg), which targets CD33 (Siglec-3), is already approved for use in acute myeloid leukemia (AML). In addition, NC318, an antibody targeting Siglec-15, is currently undergoing clinical trials[158]. Another innovative approach involves enzymatic desialylation. E-602 is a novel, first-in-class engineered human sialidase (Neu2) Fc fusion protein designed to enhance anti-tumor immunity by removing immunosuppressive sialic acid residues from glycans, which is now under development for cancer treatment. Furthermore, a dual-function PD-L1-targeting sialidase fusion molecule has entered clinical trials. The current immune therapeutics to modulate TAMs are list in **Table 1**.

Conclusions and perspectives

TAMs act as a "metabolic regulator" of neoplastic and stromal cells, such as CAFs; immune cell, such as DCs and effector T cells through metabolite exchange and metabolism-dependent signal secretion. This metabolic symbiotic relationship is key to the maintenance and continuous evolution of the TME. Given the broad implications of innate immunity in cancers, these findings will drive future work to identify molecular mechanisms connecting metabolism and TAM functions in a wide variety of diseases. Current research in the field of metabolism continues to face significant challenges. For example, the intricate metabolic crosstalk between TAMs and tumor cells complicates the accurate identification of safe and effective therapeutic targets. Moreover, the complexity of the TME leads to dynamic fluctuations in metabolites, such as lactate and some lipids within the TME. These metabolic shifts actively influence TAMs, further complicating drug design and the evaluation of therapeutic efficacy. Of note, metabolic compensation in metabolism-targeted therapies can lead to off-target effects, associated toxicities, and drug resistance. Future efforts to improve TAM targeting through strategies, such as CAR-M therapies, and to develop combination treatments based on emerging research will help advance the field of tumor immunotherapy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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